Early diagnosis of Alzheimer's disease: The role of biomarkers including advanced EEG signal analysis. An I.F.C.N.-sponsored panel of Experts

EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE: THE ROLE OF BIOMARKERS INCLUDING ADVANCED EEG SIGNALS ANALYSIS. An I.F.C.N.-sponsored panel of Experts.

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ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disease among the elderly with a progressive decline in cognitive function significantly affecting quality of life. Both the prevalence

and emotional and financial burdens of AD on patients, their families, and society are predicted to grow significantly in the near future, due to a prolongation of the lifespan. Several lines of evidence suggest that modifications of risk-enhancing life styles and initiation of pharmacological and non-pharmacological treatments in the early stage of disease, although not able to modify its course, helps to maintain personal autonomy in daily activities and significantly reduces the total costs of disease management. Moreover, many clinical trials with potentially disease-modifying drugs are devoted to *prodromal* stages of AD. Thus, the identification of markers of conversion from *prodromal* form to clinically AD may be crucial for developing strategies of early interventions. The current available markers, including volumetric MRI, PET, and CSF analysis are expensive, poorly available in community health facilities, and relatively invasive. Taking into account its low cost, widespread availability and non-invasiveness, EEG would represent a candidate for tracking the prodromal phases of cognitive decline in routine clinical settings eventually in combination with other markers. After providing a short overview of the epidemiology and markers in AD, this review aimed to explore whether advanced analysis of EEG rhythms exploring brain function has sufficient specificity/sensitivity/accuracy to screen out the risk of conversion from Mild cognitive Impairment (MCI, a condition which is prodromal to AD in a high percentage of cases) to AD as a first-level screening method.

HIGHLIGHTS

This review describes an integrated and multidisciplinary approach for the “early” diagnosis of AD.

An overview of epidemiology, genetic risk factors, and different biomarkers of AD is provided.

Analysis of EEG rhythms could represent a valid screening tool to predict AD conversion.

KEYWORDS

Alzheimer’s disease; mild cognitive impairment; dementia; AD biomarkers; EEG analysis; EEG rhythms; event-related responses; early diagnosis.

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1. Introduction

Alzheimer's disease (AD) is characterized by a progressive loss of memory and deterioration of other cognitive functions. The typical AD clinical phenotype follows a prodromal stage known as Mild Cognitive Impairment (MCI), usually characterized by memory loss (amnestic MCI= aMCI), which includes a consistent percentage (about 50%) of subjects in a stage *prodromal* to dementia (aMCI

usually to AD). The identification of reliable markers able to intercept those aMCI who are in a *prodromal* stage may allow for developing early interventions. In fact, even in the absence of a disease-modifying therapy, several lines of evidence suggest that early initiation of pharmacological and non-pharmacological treatments (including changes in lifestyle) helps maintain personal autonomy in daily activities and significantly reduces the total costs of disease management (D'Amelio and Rossini, 2012; Teipel et al., 2015; Petersen et al., 2017). Moreover, many of the clinical trials with potentially disease-modifying drugs target MCI *prodromal-to-AD* subjects, since failure has been demonstrated when full symptomatology of AD has been already developed. Therefore, early markers predicting with high sensitivity/specificity the evolution from prodromal stages to clinically overt AD are of pivotal importance. Although this goal can be partly reached with the presently available diagnostic armamentarium (volumetric MRI, PET, PET+radioligands/Lumbar puncture for amyloid and tau metabolites), all of these markers have a relatively low sensitivity to synaptic dysfunction (the very early stage of presymptomatic AD); moreover, most of them are expensive, poorly available on community health facilities and relatively invasive. Taking into account its low cost, widespread availability and non-invasiveness, electroencephalographic signals (EEG) analysis may be an excellent candidate for tracking the prodromal phases of cognitive decline in routine clinical settings. This review paper was prepared under the endorsement of the International Federation of Clinical Neurophysiology (IFCN) and is the result of an "Experts Workshop" held in Rome in June 2017. Its goal is to provide an overview of the epidemiology and genetic risk factors as well as of neuropsychological and neuroimaging biomarkers, but is particularly aimed to understand whether advanced analysis of EEG rhythms exploring brain function has sufficient specificity/sensitivity/accuracy to screen out the risk of conversion from MCI to AD as a first-level screening method.

2. Alzheimer's Epidemiology

The AD phenotype and syndrome classification has improved substantially over the last decade. The diagnosis in the preclinical phase is based largely on limited and selected data from few tertiary centers. There are few and limited population–based data on the issues of new classification systems and diagnosis anticipation. Population-based data with the use of new, including advanced markers, and old criteria originate from the Mayo Clinic Study on Aging (MCAS) as part of the study of the Rochester Epidemiologic Project (REP; Rocca et al., 2018).

In everyday clinical activity the prompt diagnosis of dementia is missed in a large number of cases using the old NINCDS-ADRDA criteria (Rait et al., 2010). This is evident comparing data from the active search in population-based studies as CFAS and EURODEM with data from files of the GPs of the national UK database (passive ascertainment based on referral). The misdiagnosis or missed diagnosis is much larger in the >80 age groups compared with lower age groups. This is relevant considering that two out of three patients with AD will be over age 85 by 2050. One of the most interesting questions is the time trend of dementia incidence. Dementia prevalence is steadily growing, caused both by the aging and increased life expectation of the general population. This is a worldwide phenomenon. China, India, Indonesia and Brazil drive these demographic changes as a result of the huge size of their population (Logroscino, 2017). Recent prevalence data from CFAS in the elderly population (older than 65) from six geographic areas in England and Wales show that dementia prevalence estimated in the period 2008-11 was almost 25% less than what was predicted based on prevalence data estimated in the period 1989-94, in the same area (Matthews et al., 2013).

Consistently, CAFS report a drop in incidence of about 20%, mainly determined by a decline in incidence among males (Matthews et al., 2016).
Similarly, in the Framingham Study a population-based investigation (Satizabal et al., 2016) has been conducted looking at dementia incidence time trends in five thousands elderly (more than 60) within the period 1977-2008, divided in four 5-year intervals. The cumulative dementia incidence rates declined from 3.6 / 100 to 2.0 per / 100 person year. Dementia declined about 44% in the more recent period only in subjects with at least high school diploma. The decline was both for AD and vascular dementia. In the same period, there was an increase in diabetes, obesity and hypertension. On the other side, there was an increase in number of hypertensive subjects with medical treatment, a reduction of stroke), a decrease in the prevalence of smoking, an increase of average levels of high-density lipoprotein (HDL) cholesterol. Furthermore, there was really a dramatic increase in education, with subjects holding a college degree going from 13 to 34 %. Several causes and possible interactions of these changes have still to be identified.
All these evidences show that –under appropriate lifestyle modifications– dementia incidence is declining in a relatively short period of time, similarly to what happened previously for myocardial infarction and stroke (Mozaffarian et al., 2015). These changes indicate that dementia is largely preventable. In the last two decades, several observational studies have shown a wide variety of potentially modifiable risk factors for cognitive impairment and dementia (Livingston et al., 2017), which have been proposed as targets for preventive strategies. In addition to cardiovascular risk factors, psychological conditions, education level, engagement in social and mentally stimulating activities, sensory changes, and lifestyle including diet, physical activity and voluptuary habits has obtained a crucial role (Panza et al., 2015; Livingston et al., 2017). The recognition of modifiable risk factors and successive intervention may be part of a population strategy that could lead to a significant decrease of about 30% of dementia cases, according to conservative estimates recently published (Norton et al., 2014).

3. Cost effectiveness of early diagnosis in Alzheimer's disease

AD was estimated in 2010 to cost about $604 billion in US annually. These costs are staggering, particularly taking into account the predictions for the growth in the worldwide number of AD cases (Wimo et al., 2013) will increase rapidly in the next decades. The global costs of dementia were estimated in the United States (US) to total $818 billion in 2015, an increase of 35% since 2010; 86% of the expenses are incurred in high-income countries. The costs of informal care and the direct costs of social care still contribute within similar proportions the total cost, whereas the cost of the medical sector is much lower. The threshold of US $1 trillion is currently being crossed (Wimo et al., 2017).
The advantage for an early diagnosis of AD in a scenario that does not permit disease modifying therapy is still debated and, in absence of such therapies, programs devoted to screen general old population for AD could appear useless. In contrast, it is generally thought that also the treatment with Choline Esterase inhibitors (ChEi) is more effective when used before widespread pathological changes have occurred (Cummings JL et al., 2008; Hogan et al., 2008).
On this field, several neuroeconomic investigations have provided reliable recommendation about the effect of an early diagnosis on the social cost and the advantage in patient management. In particular, timely detection and symptomatic intervention in AD-dementia can be cost-effective because even

though having limited efficacy, they nonetheless control symptoms enough to reduce healthcare costs and keep patients living longer in the community (Geldmacher, 2008). Moreover, a UK study based on 2007 costs estimated that cover ten years, timely detection and treatment produced savings of £3600 (US $5508) in direct costs and an additional £4150 ($6350) in indirect costs (caregiver time) per patient (Getsios D et al., 2012).

Despite the burden posed on individuals and the health care system, diagnosis of AD is clearly suboptimal. For instance, the UK National Audit Office estimates that more than half of all cases of AD in the United Kingdom are undiagnosed.

Recently, Barnett and coworkers (2014) explored the effect of an early diagnosis and interventions in the Paquid cohort. They calculated the economic effects of moving AD diagnosis from the real standard diagnosis (MMSE 18) to the previous 8 years. They applied a statistical model in which a symptomatic treatment that improve cognition by one MMSE point would produce a maximum net cost benefit when applied at the earliest time point and this effect would drop 17% for each year of delayed diagnosis. In contrast, for a scenario where a disease-modifying treatment (DMT) halting cognitive decline for one year, economic benefits would peak when treatment effects were applied two years prior to standard diagnosis. In this case the effect would be fifteen times greater than in the symptomatic one. It's clear that the modification of the clinical trajectories with both symptomatic and DMT could have enormous consequences on the general cost of AD management. This offers a challenge for all Health Services, which should be prepared to face an increasing number of subjects with dementia. Besides, when we pass to the scenario of DMT availability, the diagnosis will move from AD-dementia to pre-dementia AD states. In such condition, clinical criteria are unlikely to be appropriate and progressively more expensive investigations will be required.

4. Overwiew on AD Markers

The role of markers in the diagnosis of dementia is becoming progressively more important as the need for an "early" diagnosis is now prominent, namely a diagnosis in pauci- or asymptomatic disease stages. The concept of "MCI *prodromal* to AD" has been introduced in a manuscript from a panel of international experts (Dubois et al., 2010, 2014), showing that if neuropsychological tests are combined with information from neuroimaging (both structural and flow/metabolic), CSF analysis and genetic risk evaluation, one can predict with high accuracy the evolution to AD in MCI subjects at an individual basis or –better– MCI subjects who are already in a stage *prodromal to AD* can be promptly intercepted.

The main criterion for quality selection in this review has been focused on those markers best predicting the progression from MCI to AD in longitudinal studies, while cross-trans-sectional studies were excluded. When looking to the best evidences for each biomarker, Cochrane reviews which identify quality of the studies by means of the checklist QUADAS (Quality Assessment of Diagnostic Accuracy Studies) and STARD (Standards for Reporting Diagnostic Accuracy) were preferred whenever available

Subjects with a prodromal stage of AD (IWG2) or Mild cognitive impairment (MCI) *prodromal-to-AD* (NIA-AA) are the main targets for the employment of diagnostic/prognostic markers. MCI is a clinical and neuropsychological state in the elderly brain intermediate between normal cognition and

dementia. It is mainly characterized by objective evidence of memory impairment during a neuropsychological examination that does not yet encompass the definition of dementia. Epidemiological research suggests that aMCI is a precursor of AD, based on the high rate of progression from this state to AD. Not all MCI subjects convert to dementia, but many, between 50 and 60%, do it. The remaining individuals will either remain in the MCI condition or return to a fully normal one and never progress to dementia. To plan optimal and early therapeutic, organizational and rehabilitative interventions, aMCI diagnosis should be combined with the most reliable prognosis on the likelihood and time of progression to dementia. The MCI definition requires the following: cognitive questionnaire, screening tests (MMSE), neuropsychological evaluation - including 2 tests for episodic memory, tests for language, visuo-spatial abilities and behavioral scales with appropriate normative thresholds (Cerami et al., 2017; Costa et al., 2017) -, functional scales, neurological examination and a CDR score of 0.5. Growing evidences suggest that early diagnosis reduces health and social costs for dementia management. Moreover, MCI *prodromal* to AD is becoming progressively more frequent and is the preferred target for clinical trials with potential disease-modifying experimental drugs. Early diagnosis of the MCI *prodromal* to AD can presently be reached with a very high sensitivity and specificity by combining a number of tests (i.e. hippocampal volumetric MRI, ^{18}F-FDG PET and lumbar puncture for CSF examination). Because of their elevated costs, low availability and/or invasiveness, though, these cannot be applied to evaluate a large population sample on a nationwide scale. In a recent study by an international consortium (Cohort Studies Memory in an International Consortium-COSMIC - Sachdev et al., 2015) it was attempted to define the epidemiological boundaries of the MCI condition by a metanalysis of the published data. A prevalence of 5.9% has been estimated in a population with >60 year, with an increment of the stratified age ranges from 4.5% (60 to 69 years), to 5.8% (70 to 79 years) and 7.1% (80 to 89 years). On this basis, - even if this scenario is not accepted by all the Experts (see Petersen et al., 2018) - just for example, for the 2016 in European Community population an estimated number of about 8.000.000 MCI subjects can be predicted.

4.1 Genetic markers

Three decades of genetic research have substantially broadened our knowledge about pathogenic mechanisms leading to neurodegeneration and dementia, starting, however, from very rare forms of AD. In the 20th century, genetic linkage analysis identified three major causes underlying genetically dominant early onset forms of AD (ADAD) such as Amyloid precursor protein (*APP)*, and Presenilins (*PSEN1* and *PSEN2)* genes (Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995). Mutations of these genes represent *state markers* of the disease, since they are dominant mutations, carriers develop and transmit the disease to 50% of offspring, and penetrance is about 100%. Although ADAD has a rather clear phenotype characterized by memory loss, time and space confusion, apraxia, agnosia, troubles of language, neither the onset nor the phenotype are constant and monomorphic, and overlapping can be frequently observed between clinical phenotypes, genotypes and also pathological proteotypes (Tang et al., 2016). Several families carrying a *PSEN1* mutation have been described with involvement of frontal lobe or spastic paraplegia (Piscopo et al., 2008; Wallon et al., 2012) or extrapyramidal signs thus mimicking Lewy body dementia (Karlstrom et al., 2008; Wallon et al., 2012). Even in the large ADAD Calabrian kindreds, sharing the same *PSEN1* mutation and a classic neuropathological phenotype, at onset symptoms cluster into four different groups: apathetic, amnesic, dysexecutive, disoriented (Bruni et al., 2010) (Fig. 1A). The

APP A713T mutation leading to AD with cerebrovascular lesions (CVLs) in Calabrian families associates to both early and late onset phenotypes, also independently from homozygosity (Conidi et al., 2015) (Fig. 1B).
The multigenerational ADAD families (Tang et al., 2016) frequently reconstructed along centuries through genealogy with hundreds of affected subjects and at risk relatives represent an extraordinary and powerful model for the study of AD. All the three genes are involved in the processing of beta amyloid strongly sustain the amyloid cascade hypothesis (Schellenberg and Montine, 2012). DIAN cohort constituted by ADAD carriers has already showed that the biological disease starts in the brains decades before clinical onset (Tang et al., 2016) with the deposition of β amyloid and the alterations of the other biomarkers. The same certitude cannot be confirmed in late onset AD that is still unclear regarding etiology and pathogenesis and whose genetic component is complex and much more difficult to ascertain.
The lifetime risk to develop AD is about 10-12% (Breitner et al., 1999) and a genetic susceptibility increasing or decreasing the risk of developing the disease does exist. There are almost an infinite number of susceptibility genes for dementia. The Apolipoprotein E (*APOE*) gene with the e4 allele gives to carriers a higher risk of developing the disease, especially in women (Liu et al., 2013), shortening of the age of onset of AD not only in sporadic AD patients but also in carriers of mutations of both the *PSEN1* (Pastor et al., 2003) and of *APP* (Sorbi et al., 1995). In recent years several whole-genome sequencing studies (GWAS) have suggested that the risk of developing AD is given by the association of common polymorphisms with low penetrance and high frequency in the population and, therefore, with small effect size; although the total number of AD risk genes remains elusive there are significant evidences suggesting that their combinations may have a substantial impact on disease susceptibility, onset (Bertram and Tanzi, 2008) and progression of sporadic LOAD.
Theoretically, assessment of genetic risk could be a key to preventing or slowing the progression of the Alzheimer's disease. APOE ε4 genotype has been demonstrated as the major predictor of progression to AD in patients with aMCI (Zheng et al., 2016). However, the use of APOE genotyping is limited due to its low sensitivity and specificity, but it could be useful in combination with other markers including EEG connectivity (Vecchio et al 2018). Zheng et al. (2016) found a notable increase in plasma homocysteine (HCY) together with a significant decrease in serum brain-derived neurotrophic factor (BDNF) in aMCI - APOE ε4 patients converting to AD. Studies focused on changes in DNA methylation level (i.e. COASY and SPINT1 gene promoter regions) could be helpful to identify subjects destined to progress from MCI to AD (Kobayashi et al., 2016).
Although ADAD mutations are marker of state not of process, combined together with current biomarkers, they will allow an early diagnosis even in the preclinical phase. The implementation and evaluation of AD genetic risk markers in the prediction of MCI to AD dementia progression it is in an early phase. However, detecting new susceptibility factors with a functional impact on AD will bring about major insights into the disease pathways, and initiate new lines of research.

4.2 Neuropsychological markers

An important milestone for the modern era of AD research is the publication of the NINCDS-ADRDA clinical criteria for the diagnosis of Alzheimer's dementia, which remained the standard reference in the field for more than two decades (McKhann et al., 1984). According to the original McKhann criteria, "*neuropsychological tests provide confirmatory evidence of the diagnosis of dementia and help to assess the course and response to therapy*". Neuropsychological tests are

recommended for specific aims, such as the definition of unusual pattern of cognitive deficits, in the context of longitudinal studies or as outcome measures for drug efficacy trials. An important change took place only in the '90s, with the rise of interest in the identification of a "pre-dementia" stage of AD, resulting in the introduction of the MCI concept (Petersen et al., 1999). Among the criteria for the diagnosis of this at-risk condition for progression to dementia is the presence of an objective impairment of memory, defined on the basis of a defective test performance in comparison to an age-matched control group. In the following period this concept was extended, on the basis of the same psychometric criteria, to other cognitive domains besides long-term memory (Petersen, 2004).

The International Working Group Research Criteria (Dubois et al., 2007, 2010, 2014) and the National Institute on Aging- Alzheimer's Association workgroups on diagnostic guidelines (McKhann et al., 2011) introduced a novel approach, based on the concept of an AD continuum, rather than of disease "stages". Both set of criteria emphasize the role of markers in supporting the diagnosis of AD at the very early clinical stages, i.e. when the patient is symptomatic but does not fulfill the criteria for dementia (respectively, *prodromal AD*, or *MCI due to AD*). Within this perspective, neuropsychological tests can be considered as a "gateway biomarker" in the AD diagnostic process (Cerami et al., 2017). In the case of typical presentations of AD, the performance in episodic memory tests is crucial for early diagnosis, and is the basis for the definition of MCI or prodromal AD according to current diagnostic criteria. There is however no consensus on the most appropriate tests to be employed. Episodic memory tests are sensitive, but not specific. In addition, they are unsuitable to measure disease severity and progression as they reach floor levels early in the disease course. Tests controlling for effective memory encoding and retrieval may be particularly suitable to identify the hippocampal amnestic syndrome, which is typical of AD with the presence of a paradigmatic and specific episodic memory involvement, characterized by a diminished free recall ability, which is only marginally improved by cueing. In this regard, the Free and Cued Selective Reminding Test (FCSRT) has been used with the aim of maximizing the differentiation between the genuine hippocampal deficit of AD and age-associated memory dysfunctions, due to impaired attention, inefficient information processing, and ineffective retrieval (Grober and Buschke, 1987). The FCSRT, as well as the "bedside" 5-Word cued recall test (Dubois et al., 2002; Economou et al., 2016) increase the specificity for AD (Dierckx et al., 2009; Wagner et al., 2012). There is also evidence supporting the value of the FCSRT to predict progression towards dementia in at risk populations (Sarazin et al., 2007).

An important issue is the role of neuropsychological testing in diagnosis atypical AD presentations. The three main forms defined by the IGW-2 criteria (Dubois et al., 2014), i.e. the language, visuospatial and behavioral presentations, require specialized neuropsychological assessment for an adequate diagnostic evaluation, in particular in the early stages, for follow-up and for evaluation of treatment effects. The logopenic/phonological variant of primary progressive aphasia (PPA) is by far the most common language presentation of AD (Spinelli et al., 2017). Only very few tools have been specifically developed for the assessment of language deficits in PPA patients, and for the characterization of the PPA subtype, which is relevant for a probabilistic diagnosis of the underlying pathology. The language tests in common use (e.g. Aachener Aphasie Test (AAT), Huber et al., 1980) and the Boston diagnostic aphasia examination (BDAE) (Kaplan, 1983) have not been specifically developed for the differentiation of the subtypes of PPA, but rather for the evaluation of aphasia due to stroke. A "minimal" procedure, allowing a classification according to the current diagnostic criteria (Gorno-Tempini et al., 2011) must include:

a. a qualitative and quantitative observation of patient's speech and language during a semi-structured interview, which can be based on a complex picture description. The main parameters to be assessed are: lexical production rate and phonological/articulatory errors; disorders of fluency (pauses and repetitions); lexical typology; and syntactic structure and complexity. On this basis, it is possible to conclude for the presence or absence of motor speech disorders and agrammatism, necessary for the differential diagnosis with other PPA variants, seldom associated to AD pathology;
b. tasks of picture naming and word-picture matching to assess single word comprehension;
c. a repetition test allowing an assessment of phonological and auditory verbal short-term memory abilities, typically impaired in logopenic aphasia ;
d. sentence-picture matching tasks to assess syntactic comprehension.

The visuo-spatial presentation of AD is posterior cortical atrophy (PCA) (Crutch et al., 2017). This clinical picture is characterized at the onset by prominent visuo-spatial cognitive features, such as deficits in space and object perception, simultanagnosia, constructional dyspraxia, prosopoagnosia, oculomotor apraxia, optic ataxia and alexia. As in the case of logopenic aphasia, all these aspects can be quantified using a wide array of tests, which have been developed for the neuropsychological evaluation of focal brain damage, such as the copy of Rey's figure (Rey, 1941). An excellent screening battery, which allows to evaluate in a short amount of time the function of both ventral and dorsal visual processing pathways is the Visual Object and Space Perception Battery (Warrington and James, 1991).

Finally, a true challenge for neuropsychological assessment is the third variant of atypical AD presentation, characterized by "frontal" features (Ossenkoppele et al., 2015). The crucial issue here is the differential diagnosis with the behavioral variant of frontotemporal dementia, which requires, in addition to biomarker evidences, a detailed neuropsychological assessment. This must not be limited to classical "frontal lobe tests", such as the Wisconsin Card Sorting (Heaton et al., 1993) or the Stroop test (Stroop, 1935), but requires a comprehensive evaluation of behavioral disorders and neuropsychiatric disturbances (for example, with the Frontal Behavioral Inventory, Kertesz et al., 1997, and the Neuropsychiatric Inventory, Cummings et al., 1994), as well as an assessment of social cognition performance (see, for example Torralva et al., 2009).

To summarize, a clear definition of the cognitive/behavioral phenotype is the first step towards a biomarker-supported pathological diagnosis of AD. The identification of the very early/prodromal stages of both typical (hippocampal episodic memory) and atypical (visuo-spatial abilities, language, executive function and behavior) presentations is one of the main goals of neuropsychological assessment. There is clearly a need for harmonization of tools and procedures and for the collection of high quality psychometric data. This priority, however, should not obscure the importance to develop innovative ideas based on the advances in cognitive neuroscience research. The recent focus on pre-clinical rather than prodromal stages (Dubois et al., 2016) offers a great opportunity for the development of novel, continuous measures assessing cognitive efficiency and functional status. Taking advantage of the technological possibilities, such as those offered by smartphones and social media (Wilmer et al., 2017), is one of the many interesting developments to be explored in the next few years.

4.3 Neuroimaging markers

Advances in neuroimaging techniques, including magnetic resonance imaging (MRI) and Positron Emission Tomography (PET), have strongly contributed not only in increasing our understanding of

clinical and pathophysiological aspects of dementias, but also in improving the diagnostic confidence in clinical settings (McGinnis, 2012). MRI, thanks to its ability to image *in vivo* soft tissues non-invasively and with detailed anatomical resolution, shows high sensitivity in detecting the presence and extension of macroscopic abnormalities of the brain tissue (Bozzali et al., 2016) and in excluding alternative diagnoses that may mimic a neurodegenerative form of cognitive decline such as brain tumors, normal pressure hydrocephalus, subdural hematoma, and cerebrovascular encephalopathy. On the other hand, PET imaging has proven high sensitivity in detecting metabolic abnormalities at individual level since the early clinical stages of cognitive decline (Iaccarino et al., 2017). Additionally, novel tracers, including beta-amyloid and tau-protein ligands have become available with the potential of detecting *in vivo* specific pathological features of brain tissue degeneration (Jack et al., 2017).

Conventional MRI. Besides the exclusion of secondary causes of dementia, conventional MRI may be used to address a correct diagnosis of AD only in a proportion of cases, mainly based on assessment of regional brain atrophy. The simplest way to determine regional changes of brain volumes is to use rating scales based on visual examination of T1-weighted MR images (Scheltens et al., 1992; Wahlund et al., 2001), such as the "medial temporal lobe atrophy" MTA scale (Scheltens et al., 1992). The use of MTA has shown high accuracy in determining the severity of local atrophy in cross-sectional studies that compared AD patients against healthy controls (Ridha et al., 2007). Conversely, MTA appears to be poorly informative in detecting longitudinal volumetric changes over time (Ridha et al., 2007; Persson et al., 2017). There have been introduced specific visual rating scales also to quantify the presence and severity of macroscopic white matter (WM) abnormalities. The Age Related White Matter Changes (ARWMC) (Wahlund et al., 2001) and the Fazekas' scales (Fazekas et al., 1987) allow a simple assessment of macroscopic WM lesions. In the diagnostic suspect of AD, taking altogether the information given by MTA and WM lesion assessment, three different patterns may schematically be identified: 1) severe MTA and minimal WM abnormalities; 2) minimal MTA and severe WM abnormalities; 3) moderate MTA and moderate/severe WM abnormalities. In the first two cases, conventional MRI strongly contributes in increasing the diagnostic confidence of neurodegeneration. Although the contribution of conventional MRI remains limited in the third case, however a strict association has been recently shown between brain amyloid deposition and both presence and severity of periventricular WM lesions (Marnane et al., 2016).

Quantitative Brain Volumetrics. The development of sophisticated registration algorithms has made it possible to bring volumetric images from different subjects into a common space and to identify differences between groups (e.g., patients vs. controls) or correlations with clinical/psychometric measures, on a voxel-by-voxel level basis. For data-driven analyses, voxel-based morphometry (VBM) is one of the most popular techniques to investigate dementias (Ashburner and Friston, 2000). This approach is operator-independent and does not require any *a priori* hypothesis on the anatomical localization of the brain tissue loss (i.e., voxel-wise analysis) (Bozzali et al., 2006). Different statistical designs can be employed, which allow between-group comparisons to be performed as well as correlations between distributions of regional GM volumes and clinical, neuropsychological and behavioral variables. When applied to AD patients at different clinical stages, VBM has demonstrated a widespread pattern of GM atrophy, including not only the medial temporal lobe structures but also several other areas of the association cortex (Serra et al., 2010a, 2014). Moreover, in patients with AD and aMCI it has been shown a strict association between cognitive profiles and regional patterns of GM atrophy (Serra et al., 2010a,b, 2014). Within the early stages of cognitive decline, MCI can

also be dominated by neuropsychological deficits other than memory (i.e., non-amnestic MCI). Again, VBM has shown the ability to detect patterns of regional GM loss that fit with the non-amnestic neuropsychological profile, thus allowing a differentiation of MCI patients who are more likely to convert to other forms of dementias (Serra et al., 2013). Moreover, VBM has identified different patterns of GM volumes in association with different levels of cognitive reserve in patients with AD at different clinical stages (Serra et al., 2011).

Diffusion imaging. Diffusion imaging provides, through the measurement of diffusional motion of water molecules into brain cells, unique information to investigate the WM microarchitecture, connectivity and integrity (Basser and Jones, 2002; for a review on 'connectivity' see Rossini et al., 2019, in press). Diffusion imaging has been widely used in studies investigating MCI and AD patients (for a review, see Bozzali et al., 2016). Some of them have reported a widespread alteration of WM tissue integrity in patients with AD at different clinical stages and using both a whole brain analysis (Serra et al., 2010a; Liu et al., 2011) or focusing on specific WM tracts (Serra et al., 2012; Bozzali et al., 2012). For instance, a study based on diffusion tractography of the cingulum (i.e., the main pathway of connection between the limbic system and the rest of the brain) has shown a progressive disruption of this structure over the transitional stage from MCI to AD (Bozzali et al., 2012). Interestingly, this WM damage accounts, in combination with regional GM loss, for the cognitive features of preclinical and clinical stages of AD (Bozzali et al., 2012). A novel method of diffusion imaging analysis, called anatomical connectivity mapping (ACM), has been proposed to assess changes in structural brain connectivity across the whole brain (Bozzali et al., 2011,2013).

Functional MRI. Neuronal activity can be investigated non-invasively, but indirectly, through blood oxygenation level dependent (BOLD) functional MRI (fMRI). fMRI can be used to assess changes of brain activation in response to performance at cognitive tasks e.g., memory, visuo-spatial abilities, executive functions, emotion processing, etc). On the other hand, fMRI can be used at rest to record coherent fluctuations of brain activity over time, in the so-called resting-state fMRI technique. In this case, fMRI provides information on functional brain connectivity within specific networks, some of which have been associated with specific cognitive functions. fMRI investigations based on active tasks of episodic memory have reported, in AD, reductions of functional activity in the hippocampus and other temporal lobe areas, and increased activity in the parietal association cortex (Peters et al., 2009). Conversely, other studies have reported patterns of decreased functional activity (during memory tasks) not only in the temporal lobe but also in parietal and frontal regions (Golby et al., 2005). Studies involving patients with MCI have generally reported increased activation in brain areas related to the administered tasks (for a review, see Pihlajamäki et al., 2009). There is some evidence that the increase of functional activity might represent compensatory mechanisms against the incipient occurrence of brain atrophy (Lenzi et al., 2011).

Among various functional networks, the default-mode network (DMN) (Greicius et al., 2003) has been intensively investigated in patients with AD. This network includes the posterior cingulate cortex, the inferior parietal and the medial prefrontal cortex, and these regions are believed to be similarly modulated by cognitive tasks. A study involving patients with AD, patients with aMCI and healthy controls, has i shown that functional disconnection may precede the GM atrophy in the posterior cingulate cortex, supporting the hypothesis that atrophy (at least in some regions of AD brains) is likely to reflect a long-term effect of brain disconnection (Gili et al., 2011). In addition, DMN connectivity has been found to be modulated by individual levels of cognitive reserve (Bozzali et al., 2015), thus helping clarify the neurobiological substrate of compensation mechanisms that

delay the clinical impact of AD pathology. Recently, a modulation of connectivity due to cognitive reserve was observed also at larger scale in the brain, based on more sophisticated brain connectomics. MCI patients with higher cognitive reserve showed increased functional connectivity in a large network of fronto-parietal nodes and decreased connectivity in a network involving fronto-temporo-cerebellar nodes (Serra et al., 2017). Interestingly, this effect was clearly detectable in MCI patients only, suggesting that the cognitive reserve acts to counterbalance AD symptoms in a specific time window of the transitional stage between normal aging and dementia.

Metabolic Imaging. PET imaging is in principle capable of detecting disease processes when there is no evidence of structural changes on MRI (Phelps, 2000). ^{18}Fluorodeoxyglucose (^{18}FDG-PET) is a widely available PET tracer that reflects the local glucose metabolism as a proxy index for neuronal activity (Bohnen et al., 2012). Typical ^{18}FDG-PET finding in patients with AD is a pattern of reduced glucose uptake in temporo-parietal association areas, in the precuneus and in the posterior cingulate cortex (Iaccarino et al., 2017; Bohnen et al., 2012; Kato et al., 2016). ^{18}FDG-PET has demonstrated a high specificity in discriminating between patients with AD and healthy subjects (ranging from 70 to 90%), and between patients with AD and those with other forms of degenerative dementia (specificity of 87%) (Knopman, 2012). Available evidence supports the position that an abnormal processing of β-amyloid (Aβ) peptides is the initiating event of AD pathophysiology, which eventually leads to accumulation of Aβ plaques in the brain tissue (Hardy and Selkoe, 2002). This process occurs when individuals are still cognitively intact, many years before the occurrence of clinical manifestations of AD. Amyloid PET imaging has been proposed as a tool for early detection of AD pathology *in vivo* (Rowe and Villemagne, 2013). In AD, amyloid PET imaging has shown increased tracer binding in areas known to have high concentrations of amyloid plaques such as the medial and orbitofrontal regions, the lateral parietal and temporal cortex, the precuneus and posterior cingulate (Rowe and Villemagne, 2013). Nevertheless, β-amyloid deposition is widely present also in normally functioning brains, and disentangling the aging effect from AD pathology remains an issue, especially in cases of late-onset AD. When considering the prognostic value of PET imaging on the risk of conversion to AD, measures of brain glucose metabolism and amyloid load are both extremely powerful markers. In a longitudinal study, ^{18}FDG-PET positivity performed as the best individual predictor for AD conversion, but the combination of both, ^{18}FDG-PET and ^{11}C-PiB-PET imaging, improved classification accuracy (Iaccarino et al., 2017). Finally, although future studies are needed to clarify their specific role, PET imaging shows nowadays the potential of detecting *in vivo* specific aspects of neurodegeneration, including not only beta amyloid deposition, but also tau protein accumulation (Jack et al, 2017).

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4.4 Fluid markers

In the last two decades, several fluid markers for specific pathologic changes and non-specific markers of oxidative damage or inflammation in AD patients have been proposed and tested. Over time, the most consistent findings have been obtained with three CSF markers: the $A\beta_{1-42}$ peptide ($A\beta_{42}$), the total tau protein (T-tau) and the phosphorylated tau protein (P-tau) (Blennow et al., 2006, 2010). Although protein content is lower in cerebrospinal fluid (CSF) than in serum, CSF markers are preferred over blood/plasma biochemical markers in AD to reflect brain pathophysiology, because the brain is in direct contact with the CSF by unrestricted bi-directional flow of proteins and the CSF

is withdrawn from direct impact of the peripheral system through the restricted transportation of molecules and proteins by the blood–CSF barrier (Olsson et al., 2016). Indeed, the three CSF markers are related to the three main pathological changes that occur in the AD brain: amyloid-ß (Aß) deposition into extracellular Aß plaques, intracellular neurofibrillary tangles (NFT) formation, and neuronal loss. Particularly, in AD patients, Aβ42 is found at low concentrations due to cortical amyloid deposition, T-tau at high concentration due to cortical neuronal loss, and (P-tau) at high concentrations, reflecting cortical tangle formation: this pattern is commonly referred to as the "AD signature" (Galasko et al., 1998; Clark et al., 2003; de Leon et al., 2006; Fagan et al., 2007, 2011; Shaw et al., 2009).

There are numerous reviews on the diagnostic performance of the CSF markers, including in the early stages of AD (for a recent review see Olsson et al., 2016). In particular, combining these CSF markers adds to diagnostic accuracy, both for early identification of AD and to differentiate AD from non-AD dementias with sensitivity and specificity reaching 85–90% (Blennow et al., 2010). The CSF markers are also highly predictive of progression to AD from MCI (Hansson et al., 2006; Fagan et al., 2007; Li et al., 2007; Diniz et al., 2008; Brys et al., 2009; Mattsson et al., 2009; Snider et al., 2009; Shaw et al., 2009). Subsequently, the diagnostic criteria for AD dementia established by the NIA-AA (McKhann et al., 2011) and the research criteria by the IWG-2 (Dubois et al., 2014) recommend the use of fluid markers (reduced levels of Aβ42 and elevated levels of T-tau and P-tau in CSF), when there is a need to increase the certainty that the underlying cause of a dementia syndrome is AD. Similar recommendations for markers were presented in the most recent European Federation of Neurological Societies guidelines for the diagnosis and management of AD (Hort et al., 2010) and other dementias (Sorbi et al., 2012). In the diagnostic criteria for MCI because of AD, developed by NIA-AA, a positive Aß marker (either by amyloid-PET or CSF) together with the presence of a neuronal injury marker, such as medial temporal lobe atrophy or elevated levels of T-tau and P-tau in the CSF, indicates that the MCI syndrome may be because of AD, whereas negative Aß markers suggest that MCI is unlikely because of AD (Albert et al., 2011). The IWG-2 criteria for prodromal AD are the presence of episodic memory decline of the hippocampal type as the leading clinical symptom and positive marker evidence from either CSF or imaging that supports the presence of underlying AD pathology (Dubois et al., 2014).

Although such bulk of evidences, further research, validation, and standardization are required for a clinical routine use (for recent recommendations about the use of CSF markers in clinical practice see Herukka et al., 2017, and Simonsen et al., 2017). At this regard, worldwide standardization efforts and quality control programs, including standard operating methods for both preanalytical (e.g., lumbar puncture and sample handling) and analytical (e.g., preparation of calibration curve) procedures, together with efforts of biotechnology companies to develop highly reproducible assays on fully automated instruments are ongoing: these global standardization and harmonization measures will provide the basis for the generalized international application of CSF markers for both clinical trials and routine clinical diagnosis of AD (Blennow et al., 2014).

5. EEG markers

The human brain has about one hundred billion neurons, each establishing several thousand synaptic connections in an intricate matrix. This gigantic anatomo-functional scaffold can be modeled by myriads of network structures at micro-meso-macro-scale levels, with nodes and links that—at the

macroscale level—dynamically cooperate with time-varying aggregations via transient and rapid locking/unlocking of the orchestrated firing synchronization of spatially separated neuronal assemblies (Singer, 1990; Jung et al., 2001; Makeig et al., 2002; Fuentemilla et al., 2006). Networks continuously re-shape throughout life via plastic mechanisms mainly utilizing the Long Term Potentiation/Depression (LTP/LTD) of synaptic transmissions. These depend upon the flow and type of input from internal and external environments as well as learning/training and aging processes. Network configuration and excitability also fluctuate in millisecond time frames, according to the cyclic changes of the cortical state ("cortical uncertainty," Adrian & Moruzzi, 1939), with an impact on their instantaneous efficacy for a given task's performance. Such phenomena are reflected in the overall electromagnetic brain signals oscillating at various rhythms, which are recordable from the scalp via electroencephalography (EEG) and magnetoencephalography (MEG). Phase synchronisation (or coherence), phase-locking, entrainment, cross-frequency (or power synchrony), and phase reset of EEG rhythms measure the degrees of functional and effective connectivity between different brain areas and play a key role in the fluctuating cortical state, reflecting communication across spatially separate functional regions operating at different frequencies and cross-frequency synchronies (Buzsaki, 2005; D'Amelio and Rossini, 2012). EEG and MEG record time-varying changes of electromagnetic signals with a time resolution of milliseconds. They also follow the dynamics and hierarchies of neuronal assembly connection/dysconnection in analogy to the previously described binding/unbinding phenomena of neuronal firing phase coherence in animal microelectrodic recordings; these synchronization mechanisms are also linked with performance in cognitive functions (Uhlhaas and Singer, 2006; Buzsaki and Schomburg, 2015).

Scalp resting state EEG rhythms reflect the summation of oscillatory membrane post-synaptic potentials generated from cortical pyramidal neurons, which play the role of EEG sources. Based on biophysical considerations, these sources were estimated as extended several squared centimeters (Nunez and Srinivasan, 2006; Srinivasan et al., 2007). These potentials can be considered as the oscillatory output of the resting state cortical system, while inputs were afferents coming from other cortical neural biomasses and thalamo-cortical neurons and neurons belonging to ascending reticular systems (Nunez and Srinivasan, 2006).

Stationarity of resting state cerebral system (as opposed to nonstationarity) means that statistical features of scalp EEG rhythms are constant during recordings. Stationary condition can be observed for relatively short periods usually not longer than tens of seconds (Blanco et al., 1995) during which EEG rhythms can be examined by classical linear frequency analysis (Kaplan et al., 2005; Nunez, 2000).

In Clinical Neurophysiology, frequency analysis of scalp EEG rhythms reveals most spectral content under 50 Hz in standard physiological conditions as scalp and skull do act as spatial and frequency filters. Indeed, EEG rhythms can be investigated at higher frequency bands, e.g. 100-250 Hz, using intracranial or MEG recordings that eliminate the skull filtering effects. In an ideal spectral analysis of scalp rsEEG rhythms, frequency bands of interest should be related to peaks in power density spectrum to denote relevant neural process (Lopes da Silva, 2013). EEG frequency analysis can be performed by many different procedures. We can arbitrarily distinguish two classes of EEG markers such as "synchronization" and "connectivity" (Babiloni et al., 2016a).

Linearity and non-linearity is the behavior of a neural circuit, in which the output signal strength varies in direct or non-direct proportion to the input signal strength respectively. Herein we used the term "synchronization" to denote nonlinear oscillatory components of the brain system as a reflection

of a collective oscillatory behavior of cortical neural populations generating EEG rhythms (Boccaletti et al., 2002). To produce scalp EEG rhythms, this "synchronization" mechanism must occur at a macroscopic spatial scale of some centimeters. Synchronizing neural populations in the cerebral cortex are the main source of scalp EEG rhythms in both resting state and task-related conditions.
Typical linear characteristics of scalp EEG rhythms are power density/amplitude and phase. Magnitude and topography of power spectral density computed from scalp EEG rhythms is the most used marker of cortical neural synchronization for clinical and research aims. It is often computed by Fast Fourier Transform (FFT) from EEG epochs free from artifacts. Alternative advantageous procedures use parametric autoregressive models and wavelets analysis (Blinowska and Zygierewicz, 2012).
Spectral analysis of EEG rhythms is typically done at fixed frequency bands. There is a promising convergence of spectral analysis results of EEG rhythms in patients with AD. Compared to seniors with intact cognition (Nold), these patients show widespread increase in δ and θδ power density; posterior decrease in α and β power density with frequency lowering of α power density peak (Adler et al., 2003; Jelic et al., 2000; Nishida et al., 2011; Scheeringa et al., 2012; van der Hiele et al., 2007). Nonlinear measures of "synchronization" markers pointed to a complexity loss of cerebral dynamics in AD in the same frequency bands (Besthorn et al., 1995; Jelles et al., 1999; Pritchard et al., 1994; Stam et al., 1995, 1996; Woyshville et al., 1994; Dauwels et al., 2010a; Azami et al., 2017a for a review).
Scalp topography of EEG rhythms reflects the summation of EEG activity generated by frontal, parietal, occipital, and temporal source activities with poor spatial resolution of several centimeters. Compared to scalp EEG mapping, EEG source estimation presents the advantage that the cortical generators of EEG activity may be approximately disentangled. Of note, EEG source estimates are approximations of intracerebral neural current flows.
Both nonlinear and linear mathematics can estimate neural current density of EEG cortical sources (Valdés-Sosa et al., 2009; Gramfort et al., 2013). These procedures model 3D tomographic patterns of EEG cortical generators into a spherical or an MRI-based head model representing electrical properties of cerebral cortex, skull, and scalp, typically co-registered to Talairach brain atlas (Talairach and Tournoux, 1988; Yao & He, 2001; Pasqual Marqui 2002, 2007a,b). Source localization procedures estimate the current intensity of all dipoles (e.g. hundreds to thousands) of cortical model to explain scalp EEG amplitude/power density. These solutions are mathematically regularized to account the fact that the EEG inverse problem is under-determined and ill-conditioned.

Practically speaking, EEG data analysis may be divided into a two-step process: first, the signals recorded from all sensors are 'de-noised', that is, sensor noise and electromagnetic signals generated by unwanted sources are eliminated to the greatest possible extent; second, the current density distribution or parameters of interest are estimated from the cleaned sensor recorded signals.
This phase, sometimes called preprocessing, is devoted to the extraction of the source under study from the whole population of electromagnetic sources, including also the artefactual ones. The first step aims at improving signal-to-noise ratio by excluding portions of highly noisy data. This step includes two tasks, almost independent of the particular source under study, thus the digital signal processor (DSP) before writing the data to the disk may just accomplish them: electromagnetic signals are examined in order to exclude the portion of the data corrupted by: 1) analog to digital (ADC) overflows or by noise or possible instrument failures; 2) subject head movements or eye movements.

The next step maximizes the signal-to-noise ratio by trying to separate, as much as possible, the signal from the noise using information on the specific source under study. In some cases, it is possible to observe neural activity synchronization by supplying to the subject an external stimulus, or instructing the subject to perform a specific task. Asking to repeat this task many times and triggering the onset of analysis on the task onset, an average may be obtained over all the epochs. In this way, only the electromagnetic field originated by a source time-and-space correlated with the task is left unchanged, while all other signals are reduced by a factor $1/\sqrt{N}$, where N is the number of averages.
Given the high relevance of analyzing resting state activity, alternative procedures to enhance the signal to noise ratio were developed including Blind Source Separation (BSS) methods such as Independent Component Analysis - ICA (Hyvarinen et al., 2001) and semi-BSS such as Functional Source Separation – FSS (see Fig. 2) (Tecchio et al., 2007; Porcaro and Tecchio, 2014).
A relevant step relates the determination of the current density distribution inside the brain, especially in some region of interest. The diverse approaches to solve the so-called inverse-problem range from single and multiple dipoles (Scherg and Berg, 1991), to distributed sources, which include Multiple Signal Classification – MUSIC (Mosher et al., 1992), the recursively applied and projected-MUSIC, RAP-MUSIC (Mosher and Leahy, 1999), the minimum norm estimates, MNE (Hämäläinen and Ilmoniemi, 1994) and the Low resolution brain electromagnetic tomography – LORETA (Pascual-Marqui et al., 1994). Furthermore, spatial filtering procedures, like beam forming (for example synthetic aperture magnetometry – SAM (Vrba and Robinson, 2001), are also alternatives.
Given the side effects in solving the inverse problem, which depends on biophysical properties external to EEG-MEG information and in part unknown (proper conductivity of diverse extra-cerebral tissues), neuroscientific community spends huge efforts to extract the information of interest from the identified sources derived from BSS and semi-BSS methods.
In both cases stronger analysis tools exploits graph theory (Miraglia et al., 2017), which returns indicators of the balance between the local connectedness and the global integration of a network mainly concentrating the evaluation on the connectivity features of the involved regions. Approaches concentrating on the dynamic features of the neuronal activity include the power estimate in diverse oscillatory frequency ranges and non-linear measures assessing ether the complexity of the signal (Escudero et al., 2015) or its fractal dimension (Smits et al., 2016).

6. The relevance of EEG in AD investigation

6.1. Baseline EEG

There is a vast literature on EEG abnormalities in pathological brain aging (for a review see Rossini et al., 2006). Compared to cognitively intact elderly (Nold) subjects, AD patients contain excessive $\delta\delta$ and a significant decrement of posterior α rhythms (Huang et al., 2000). Similarly, MCI display a significant decrease of α power compared to Nold (Koenig et al., 2005). Furthermore, a prominent decrease of EEG spectral coherence in the α band in AD has been reported (Jelic et al., 2000; Adler et al., 2003).
The EEG θ power was found to be higher in aMCI who will convert to AD. In fact, a high predictive accuracy of baseline EEG features for predicting future decline was found (Prichep et al., 2006). Furthermore, the analysis of EEG coherence (the phase different of the oscillations of a given frequency at two different electrodes) has been shown to contribute to the differentiation of AD from

Nold (Adler et al., 2003) and to the prediction of aMCI conversion to AD (Jelic et al., 2000). However, findings were usually significant only at a group level (de Haan et al., 2012a); moreover, relatively small samples were investigated with a briefer than required follow up. Despite such limitations, an important review (Dauwels et al., 2010a) has summarized the progresses in the diagnosis of AD: generalized slowing of the spectral profile, reduced complexity and perturbations in EEG.

Similar features of EEG sources with some attenuation in amplitude as seen in AD patients were also observed in MCI subjects (see a review in Babiloni et al., 2016a; Canuet et al. 2012). δThese findings were confirmed by an independent approach based on minimum-norm depth-weighted estimation (Hsiao et al., 2013). Relative to aMCI subjects, AD patients pointed to reduced activity in precuneus, posterior cingulate, and parietal regions as well as increased activity in δ or θ δsources in inferior parietal, medial temporal, precuneus, and posterior cingulate (Hsiao et al., 2013).

Cross-validation of EEG source solutions was successfully done with correlation study with patients' clinical/cognitive status and other AD markers. In AD subjects, clinical symptoms were positively correlated with abnormalities in β, α, and δ δsource activities (Dierks et al., 1993; Babiloni et al., 2009). Global cognitive status as revealed by MMSE score correlated negatively with δ/θ δsource activity and positively with α source activity (Babiloni et al., 2011, 2013, 2015; Gianotti et al., 2007; Canuet et al., 2012).

Occipital, temporal, and parietal α source activities were maximum in aMCI patients with greater hippocampal volume, while they were intermediate in those with smaller hippocampal volume, and minimum in AD patients (Babiloni et al., 2009). Also, widespread α source activity was positively related to the volume of cortical gray matter in aMCI and AD subjects, while a negative correlation was found with widespread activity in δδ sources (Babiloni et al., 2013). In these subjects, there was a positive correlation between occipital-parietal α source activity and corresponding gray matter volume (Babiloni et al., 2015). Moreover, it was shown a negative correlation between EEG α dipolarity (e.g., uniformity of alpha potential distribution) and p-tau or p-tau/Aβ in cerebrospinal fluid in AD (Kouzoki et al., 2013). δ

6.2. Evoked-related potentials

ERPs are brain potentials time-locked to a sensory, cognitive, or motor event (Blackwood and Muir, 1990; Luck, 2014; Peterson et al., 1995). The ERP technique usually involves averaging brain responses over a large number of experimental trials to increase signal-to-noise ratio. The resulting waveforms are informative about the time course of sensory and cognitive processes with high temporal resolution and provide spatial information about the location of the generating structures. ERPs allow studying neural correlates of information processing including sensory-motor and perceptual processes as well as higher cognitive operations such as decision making (Howe et al., 2014).

Among the various ERPs waves, the P300 component has the longest history in clinical applications and it is the most extensively used potential to study dementia and aging. It is a relatively large (10–20 μV), scalp-positive ERP component that peaks around 250ms to 500 ms elicited by auditory, visual, or somatosensory stimuli (Polich and Kok, 1995), and is most often investigated using the so-

called “oddball” paradigm where a train of frequent and irrelevant (standard/non-target) stimuli is interspersed with random, infrequent and task-relevant (target) stimuli that have to be detected (Polich and Criado, 2006; see Rossini et al 2006 for a review). P300 amplitude has been linked with memory processes but is perhaps more sensitive to the amount of attentional resources engaged during the task (Wickens et al., 1983; Gonsalvez and Polich, 2002). P300 latency indexes stimulus classification speed (Kutas et al., 1977), reflects stimulus more than response processing (Duncan-Johnson, 1981; McCarthy and Donchin, 1981), and is generally independent of behavioral response time (Verleger, 1997; Ilan and Polich, 1999). Hence, peak latency can be used as a motor-free measure of cognitive function and has been found to be negatively correlated with mental function in normal subjects: shorter latencies are associated with superior cognitive performance from neuropsychological tests of attention and immediate memory (e.g., Polich et al., 1983, 1990; Polich and Martin, 1992; Stelmack and Houlihan, 1994; Reinvang, 1999), while increased latency is found in normal aging and increases further in dementia (Polich et al., 1986; Fjell and Walhovd, 2001;Polich, 1997).
In general, several previous studies consistently reported a prolonged P300 latency in AD patients compared to age-matched healthy controls (Pedroso et al, 2012); in particular it was found to be sensitive to deterioration of language, memory, and executive functions (Lee et al., 2013). Although the majority of P300 studies in AD focused on its latency, changes in its amplitude have also been found (Parra et al., 2012; Hedges et al., 2016) with sensitivity and specificity above 80% (Juckel et al., 2008). Two recent meta-analyses reported strong evidence that P300 latency can reliably differentiate between groups of MCI patients and controls (Howe et al., 2014; Jiang et al., 2015). Moreover, Jiang et al. showed shorter P300 latency and larger amplitude in stable MCI patients compared to MCI *prodromal to* AD (Jiang et al., 2015).
Concerning other types of ERPs evidence shows that early components are usually less affected in AD, while later potentials reflecting higher cognitive processes, such as the above mentioned P300 component, could be more effective for detecting the progression of cognitive decline and attention deficits: in fact, a decreased P600 and N400 repetition effect and also a delayed N200 latency can be detected consistently in the early stage of the disease therefore providing an useful marker to predict the conversion from MCI to AD (Horvath et al., 2018).
Finally, it’s noteworthy to highlight that the sensitivity and the specificity of ERP measurements showed great variability in the literature; therefore their diagnostic validity is considerd relatively poor. However, recent studies using promising clinical ERP approaches presented prediction accuracies of MCI/ AD progression in the 85–95% range (Bennys et al., 2007; Olichney et al., 2008; Chapman et al., 2011). It can be concluded that besides their theoretical interest, there is an urgent need to standardize ERP assessment procedures in order to obtain results that allow direct comparisons across different studies and laboratories.

6.3. Attention and working memory-related EEG features

EEG signals associated with selective attention and working memory may detect very early and subtle changes in cortical network function at baseline in cognitively intact elderly individuals, to identify initial phases of subsequent cognitive deterioration. In a recent study reported, participants were evaluated with an extensive neuropsychological battery (Giannakopoulos et al. 2009): those with a CDR score of 0.5 but no dementia and a score more than 1.5 standard deviations below the age-appropriate mean in any of the previously mentioned tests were confirmed to have MCI. Eighteen

months after the baseline evaluation, only control subjects underwent cognitive reassessment with the same neuropsychological battery. Participants were placed in the dCON group at follow-up if they had a performance of 0.5 standard deviation lower than that at inclusion for two or more neuropsychological tests. The final sample included 55 individuals in the sCON group, 42 in the dCON group, and 45 in the MCI group. Continuous EEG was recorded during a simple attentional and a 2-back working memory task (Deiber et al., 2009). The Laplacian-transformed EEG signal was segmented into epochs of 5500 ms, starting 1500 ms before stimulus onset. ERPs were obtained by stimulus-locked averaging of the signal with a 200 ms pre-stimulus baseline correction. To detect and characterize the event-related EEG oscillations whose latency and frequency ranges are not known a priori, a time-frequency (TF) analysis based on a continuous wavelet transformation of the signal was applied (complex Morlet's wavelets). Analysis was performed in the θ, α and β frequency bands. Inter-trial coherence (ITC) is a time-frequency domain measure of event-related phase locking across trials, also referred to as phase-locking factor. ITC values range from 0 to 1, with higher values indicating higher coherence of the phase of oscillations across trials. ITC analysis was performed in the θ (4-7 Hz), α (8-13 Hz) and β (14-25 Hz) frequency bands (for review see Deiber et al., 2015). ERSP (Event-related spectral power) and ITC (inter-trial coherence) were separately analyzed within the θ, α and β frequency bands over the 9 most posterior electrode sites where their amplitude was maximal. In both tasks, stimulus presentation elicited a transient increase of θ power (ERS) followed by a decrease of α and β power (ERD). An increased α and β ERD as well as decreased β ITC during the successful performance of simple attention and working memory tasks are associated with the subsequent development of neuropsychological deficits in healthy elderly controls. In the α range, the posterior ERD was enlarged in dCON and MCI as compared to sCON, suggesting an increased mobilization of resources engaged for attention and working memory in these groups. In the presence of preserved task performances, such increases were usually interpreted as compensatory phenomena related to the necessity to enhance the activation of the memory networks in order to guarantee accurate task achievement. Alternatively, the increased activation could represent an early sign of loss in brain efficiency. Modulations in the β range were less obvious than in the α range. The beta ERD was of higher amplitude in dCON than sCON and MCI, but did not differ between sCON and MCI. This parameter (decrease of β activity) is determined by exogenous, bottom up factors (Engel and Fries, 2010). Consistent with this idea, the increase of β ERD in dCON as compared to sCON can reflect an enhancement of attentional recruitment devoted to stimulus processing.

Inter-trial coherence is particularly sensitive to cognitive decline in the β frequency range during working memory activation, since this index was able to differentiate two cognitive levels within the control group, in contrast to θ and α phase-locking indices. Fine-tuning regulation within higher β frequency ranges, shown to relate to attentive behavior, would be affected in the very early phases of cognitive decline (Wrobel et al, 2007).

6.4. Event-related synchronization/desynchronization (ERS-ERD)

In the analysis of Event-related potentials, the early and late positive and negative potentials were studied in the time domain as the components named N100, N200, P200, P300, late positive potential, etc. Event-related potentials do not just have time-related changes, but these potentials also have frequency content properties. It is possible to analyze the frequency specific changes related to the function by different methodologies. The main aim in the analysis of frequency-specific changes is to find out the increase or decrease of the power spectrum in a specific frequency band and also to

find out phase information of this frequency band related to the given stimulation/task. Event-related increase in a specific frequency band is called Event-Related Synchronization (ERS) whereas event related decrease in a specific frequency is called Event-Related Desynchronization (ERD). ERS/ERD analysis was first introduced by Pfurtscheller and Aranibar (1977) and by Pfurtscheller and Lopes da Silva (1999). Klimesch (1999) reported that event-related upper alpha desynchronization is positively correlated with long-term memory performance, whereas an increase of ERS is positively correlated with the encoding of new information. Başar (1980) on the other hand mainly focused on the event-related increase of responses in a specific frequency band and called these responses as Event Related Oscillations. Furthermore, the role of pre-stimulus activity to post-stimulus responses both by analysis of power and phase information of the signal were shown (Başar, 1998, 1999) and the dynamics of event-related oscillations and the evoked power spectrum, digital filters, phase locking factors and event-related coherences for a specific function were explored in detail. Delorme and Makeig (2004) proposed their open toolbox to analyze the event-related desynchronization and synchronization and as well as inter-trial coherence, which is a measure of phase locking factor. During the analysis of time and frequency changes of event-related potentials, it is crucial to analyze all frequency bands with taking into consideration the change of event-related power spectrums and phase locking factors. In the last decade, researchers analyzed event-related time-frequency dynamics to find out the electrophysiological biomarkers for AD. Table 1 represents the event-related time-frequency dynamics of AD patients.

Event-Related δ Responses: a decrease of digitally filtered δ responses is found in AD patients in comparison to healthy controls. Several researchers showed increased δ response correlated with the increased cognitive load (Güntekin and Başar, 2016). In AD the differentiation between "target" and "non-target" responses in δ response was not found as in controls, but there was a δ response decrement during both visual and auditory oddball paradigms (Caravaglios et al., 2008; Yener et al., 2008, 2012). Furthermore, the decrease of δ response was correlated with the decrease of frontal brain volume (Yener et al., 2016). MCI patients had also decreased δ responses during "oddball paradigm" (Kurt et al., 2014; Yener et al., 2013). Furthermore, there was a gradual decrease in δ responses being higher in healthy elderly controls and lower in MCI and the lowest in AD (Yener and Başar, 2013).

Event-Related θ Responses: θ responses were mainly increased in frontal-central areas during cognitive paradigms. θ ERS is positively correlated with the encoding of new information (Klimesch, 1999), increased θ power and θ phase locking was observed during working memory paradigms (Klimesch et al., 1997; Başar et al., 2001; Sauseng et al., 2010). Alzheimer's and MCI patients had abnormalities in θ response due to their cognitive decline (Cummins et al., 2008; Deiber et al., 2009, 2015). Deiber et al. (2009) showed that progressive MCI had reduced baseline induced θ power than stable MCI and healthy controls during N-back task. In a recent study Deiber et al. (2015) reported decreased θ ERS in MCI patients in comparison to healthy controls. Caravaglios et al. (2010) showed that AD patients had increased prestimulus θ activity and reduced event-related θ power in comparison to healthy controls during auditory oddball paradigm.

Event-Related αResponses: α response has an important role in sensory, cognitive and memory processes (Klimesch, 1999). Although Klimesch's inhibition theory had high acceptance in the research area, many studies are showing that increase of α response and/or α ERS has essential functional correlates, including sensory and memory functions (for a review see Başar, 2012; Başar and Güntekin, 2012). α ERD was reduced in healthy aging subjects (Gevins et al., 1997, 2000). Babiloni et al. (2000) during movement related task showed an abnormal preponderance during both

movement related β ERD and post-movement β and α ERS values in AD. In a MEG study, Babiloni et al. (2005) reported delayed α ERD latency and increased α ERD peak in patients with dementia in comparison to healthy young and elderly subjects during the visual delayed choice reaction task. On the other hand, Karrasch et al. (2006) found reduced ERD in AD patients during auditory-verbal Sternberg memory task. In a recent study Fraga et al. (2017) also reported decreased α ERD in patients with MCI and AD in comparison to healthy controls during N-Back task. To our knowledge there is only one study that analyses event-related phase locking α responses in MCI(Deiber et al., 2015) that showed decreased α phase locking in MCI patients in comparison the healthy controls. New researches with including large patient groups are needed for understanding the dynamics of α responses in AD patients.

Event-Related βResponses: β responses were mainly related to sensory-motor functions, these responses are depressed during voluntary movement and motor imagery. However, the researches performed in the last decade have shown that β responses were also related to cognitive and working memory functions (Tallon-Baudry et al., 1998; Onton and Makeig, 2005; Ravizza et al., 2005; Güntekin et al., 2013). Missonnier et al. (2007) found that β ERS was lower in progressive MCI and AD in comparisons to stable MCI and healthy controls during attentional detection task. Güntekin et al. (2013) showed that healthy controls had higher β phase locking and power during target stimulation in comparisons to "non-target" simulation, whereas this was not the case for MCI patients who had reduced β phase locking and power during auditory oddball paradigm. Deiber et al. (2015) had also showed reduced ERS and β phase locking in MCI patients in comparisons to healthy controls during N-Back task.

Event-Related γ Responses: Evoked and induced γ responses play an important role both in sensory and cognitive processes. The increase of γ responses was reported during increased attention, memory processes, face and emotional picture recognition (Başar-Eroglu et al., 1996; Keil et al., 1999; Singer, 1999; Tallon-Baudry and Bertrand, 1999; Herrmann et al., 2004; Jensen et al., 2007; Başar, 2013; Güntekin and Başar, 2014). Osipova et al. (2006) and Van Deursen et al. (2011) found increased γ responses in AD patients in comparison to healthy controls during auditory steady-state responses. Kuriomoto et al. (2012) analyzed the ERS/ERD in AD patients during Sternberg paradigm and reported that AD patients had reduced γ ERD. On the other hand, Başar et al. (2016) analyzed the filtered γ responses in three different sub frequency γ bands and four different time windows during visual oddball paradigm. These authors found that healthy controls had higher γ responses during 0-200 ms in comparison the AD patients, whereas AD patients had higher late γ responses. Both sensory and cognitive paradigm elicits early γ phase locking. Differentiation between sensory and cognitive paradigms was found in later time windows (200-400 ms and 400-600 ms) (Başar et al., 2015). Therefore the γ responses should be analyzed in different time and frequency windows Analysis of ERD/ERS and phase locking of γ responses in AD patients during different sensory and cognitive paradigms are still needed to see the differentiation of γ responses in AD patients and healthy controls. Early and late γ responses should be analyzed separately to find out the differentiation of γ responses in AD patients comprehensively.

6.5. Nonlinear EEG analysis

The nonlinear behavior of the brain activity and its reflection in electrophysiological recordings such as the EEG has attracted substantial attention since the early 80's (Jeong, 2004; Stam, 2005; Hornero et al., 2009). The reasons were twofold. Firstly, the emergence of methods based on Chaos Theory

and their promise to achieve a deterministic characterization of complex time series (Grassberger and Procaccia, 1983; Wolf et al., 1985). Second, the fact that multiple neural processes are governed by nonlinear phenomena and such nonlinear dynamics are essential for healthy, adaptive cortical activity, up to the point that abnormal nonlinear dynamics has been related to a number of brain diseases (Breakspear, 2017).

The early application of nonlinear methods based on Chaos Theory to spontaneous EEG activity in AD showed lower correlation dimension (D2) (Grassberger and Procaccia, 1983) and largest Lyapunov exponent (L1) (Wolf et al., 1985) values than control subjects (Jeong, 2004). These findings were interpreted as a reduction in number of variables needed to describe the dynamics of the EEG (D2) and a loss of flexibility in information processing (L1). This is because D2 is a measure of the geometry of the attractor that describes the EEG signals whereas L1 accounted for how much similar activity diverged over time (Jeong, 2004). Despite their different focus on static and dynamic properties of the EEGs, the results of both D2 and L1 were associated with a reduction of complexity in EEG activity due to AD (Jeong, 2004). Such interpretation of AD as a disease affecting the complexity of EEG signals is still valid today (Garn et al., 2015; Smits et al., 2016; Azami et al., 2017a).

Nonetheless, the application of approaches based on Chaos Theory, such as D2 and L1, to EEG activity was quickly dismissed due to major methodological issues. This led to a reexamination of the field, which resulted into two alternative, yet probably more profound, research directions (Stam, 2005):

(i) The characterization and modelling of non-linear dynamics in general, in contrast to only chaos.

(ii) The development of novel nonlinear measures more suitable for application to noisy and multivariate recordings such as the EEG.

Methods of nonlinear EEG analysis can be categorized into three main groups:

- Fractal dimension metrics, including Katz and Higuchi's definitions (Higuchi, 1988; Katz, 1988).
- Irregularity estimators, including sample entropy (Richman and Moorman, 2000) and permutation entropy (Bandt and Pompe, 2002).
- Multiscale metrics (Humeau-Heurtier, 2015), including multiscale sample entropy (Costa et al., 2005) and derived approaches such as multiscale dispersion entropy (Azami et al., 2017a).

The concept of fractal dimension refers to a non-integer dimension of a geometric object. Hence, metrics such as Katz and Higuchi's fractal dimension are conceptually related to D2. However, a crucial difference with D2 is that these fractal dimensions are computed in the time domain rather than requiring the reconstruction of the signal attractor, thus making them faster (Esteller et al., 2011). These metrics have been applied to spontaneous EEG activity in AD showing that patients had reduced fractal dimension compared to healthy controls (Henderson et al., 2006), especially in temporal-occipital regions (Smits et al., 2016).

A prolific and powerful framework for the nonlinear characterization of EEG activity is that of information theory and entropy measures. In this context, metrics such as sample entropy (SampEn) can be seen as conditional entropy estimators as measures of the rate of production of information within a signal (how much information previous samples of the time series provide about the future points) that indicate its level of predictability (Faes et al., 2015). Entropy metrics have been used to analyse spontaneous EEGs in AD and in MCI. The results showed reduced irregularity in AD

patients' EEG activity. Nonetheless, these results must be taken with caution due to the reduced size of the sample used in a number of those publications and the fact that the ability to distinguish between patients and controls may depend on the values of the parameters used in the nonlinear metrics (Simons et al., 2018).

The third major category of nonlinear measures are those related to the multiscale behavior of signals and the concept of complexity, which is here understood as sophisticated behavior beyond that of both fully predictable and deterministic systems and that of merely random oscillations (Costa et al., 2005; Yang and Tsai, 2013). Thus, completely ordered (i.e., predictable) or random systems are not physiologically complex (Goldberger et al., 2002). A working measure of complexity was proposed by quantifying entropy (originally SampEn) over multiple temporal scales obtained from "coarse-grained" versions of the signals under analysis (Humeau-Heurtier, 2015; Azami and Escudero, 2018a, 2018b). This method was called multiscale (sample) entropy (MSE) (Costa et al., 2005) and it has inspired the application of entropy metrics in a multiscale way (Humeau-Heurtier, 2015; Azami et al., 2017a).

MSE has been applied to reveal significant differences at a range of temporal scales between the EEG activity of patients with AD and controls (Escudero et al., 2006; Yang et al., 2013; Coronel et al., 2017). The results indicate that the spontaneous EEG activity of AD patients is less complex than that of controls at short temporal scales (associated with higher frequencies) but this tendency reverses at longer temporal scales (related to lower frequencies) where the AD patients seem to have higher complexity (Escudero et al., 2006; Yang et al., 2013). Similar results have been obtained with multiscale dispersion entropy (MDE) (Azami et al., 2017b). This finding poses intriguing questions about the dependency of the complexity of brain activity on the temporal scales and frequency range under analysis. These issues have begun to be investigated recently (Courtiol et al., 2016; Azami et al., 2017b) but further research is needed to obtain a comprehensive interpretation of the application of multiscale methods to EEG signals and their relationship with other brain activity such as connectivity (Stam, 2005). This could be complemented with the use of appropriate computational models of EEG activity that would allow the inspection of the dependencies between structural and functional connectivity, diverse nonlinear estimators and biophysical parameters (Escudero et al., 2015; Ibanez-Molina et al., 2018).

Arguably, one of the limitations of the nonlinear methods surveyed so far is that they are applicable to single (univariate) signals only. Multivariate versions have become recently available (Ahmed and Mandic, 2011; Labate et al., 2013; Azami et al., 2017a; Azami and Escudero, 2017; Deng et al., 2017) but their use to inspect EEG activity is still in its infancy.

Finally, it is worth mentioning that most results come from spontaneous recordings but the recent availability of methods applicable to short time series enable the nonlinear analysis of EEG activity recorded during tasks (Morison et al., 2013; Garn et al., 2015; Timothy et al., 2017), something that could result in increased sensitivity and/or specificity to early AD.

6.6. Graph Theory Application and brain connectivity methods

Time series of cortical electric neuronal activity estimated with the eLORETA algorithm can be used for estimating cortical connectivity, based on the following informal definition: "Two places are functionally connected if their activity time series are similar" (Worsley et al., 2005). However, from a formal point of view, there are many different ways to define similarity between signals.

The methods proposed is performed using the exact low resolution electromagnetic tomography eLORETA (Pascual-Marqui et al., 2011). The eLORETA algorithm is a linear inverse solution for

EEG signals that has no localization error to point sources under ideal (noise-free) conditions (Pascual-Marqui, 2002). The connectivity values are obtained by Lagged Linear Coherence algorithm as a measure of functional physiological connectivity (Pascual-Marqui, 2007a, 2007b). Based on the scalp-recorded electric potential distribution, eLORETA is used to compute the cortical three-dimensional distribution of current density (source localization). The description of the method together with the proof of its exact zero-error localization property are described in Pascual-Marqui 2007 and 2009 (Pascual-Marqui, 2007b, 2009).
Several recent studies from independent groups (Canuet et al., 2011; Barry et al., 2014; Aoki et al., 2015; Ikeda et al., 2015; Ramyead et al., 2015; Vecchio et al., 2014b, 2014c, 2015, 2016b) supported the idea of a correct source localization using eLORETA, even with the standard 20-channel EEG montage (10-20 system).
Via an individual analysis, brain connectivity can be computed by eLORETA software in the regions of interest (ROIs) defined according standardized Brodmann areas for left and right hemispheres (Talairach and Tournoux, 1988). Intracortical Lagged Linear Coherence, extracted by "all nearest voxels" or those in a sphere of 19 mm radius method, selected on the basis of the number of considered nodes (Pascual-Marqui 2007a, 2011), can be individually computed between all possible pairs of ROIs for each of EEG frequency bands (Kubicki et al., 1979; Niedermeyer and da Silva, 2005): δ, alpha 1, alpha 2, beta 1, beta 2, and gamma. Then, eLORETA current density time series of each Brodmann area is used to estimate the functional connectivity. The Lagged Linear Coherence (LagR) algorithm has been implemented in eLORETA as a measure of functional physiological connectivity not affected by volume conduction and low spatial resolution (Pascual-Marqui, 2007a).
Network analysis requires that the original empirical data be represented in the form of a graph. This graph can be weighted or unweighted, and it can be directed or undirected. The first step is to decide what can be considered as a node, and what can be considered as a link (Stam, 2014). Core measures of graph theory can be computed with http://www.brain-connectivity-toolbox.net (Vecchio et al., 2014b; Miraglia et al., 2015, 2016) and represents the brain processes of segregation and integration. Segregation refers to the degree to which network elements form separate clusters and correspond to clustering coefficient (C) (Rubinov and Sporns 2010), while integration refers to the capacity of the network to become interconnected and exchange information (Sporns 2013), and it is defined by the characteristic path length (L) coefficient (Rubinov and Sporns 2010).
The mean clustering coefficient is computed for all nodes of the graph and then averaged (Onnela et al., 2005; Rubinov and Sporns, 2010). It is a measure for the tendency of network elements to form local clusters (de Haan W et al., 2009). Starting by the definition of L (Onnela et al., 2005; Rubinov and Sporns, 2010), weighted characteristic path length L^w (Onnela et al., 2005; Rubinov and Sporns, 2010) represents the shortest weighted path length between two nodes.
Small-worldness (SW) parameter is defined as the ratio between normalized C and L - C^w and L^w- with respect to the frequency bands. For example, to obtain individual normalized measures, in previous studies the values of the characteristic path length and of the clustering coefficient were divided by the mean obtained by the average values of each parameter in all EEG frequency bands of each subject (Vecchio et al., 2018,). Of note, it should be stressed that a normalization of the data with respect to surrogate networks could not be done due to the weighted values of the considered networks. Is the "graph theoretical" model superior to other types of EEG analysis in the AD diagnostic context? In order to answer this question the same type of classifier was compared to other kinds of methods of EEG analysis currently used for AD studies, applied to the same EEG epochs

utilized for graph valuation, namely spectral coherence and power spectrum. The most significant result was obtained when analyzing the power density spectrum on all available subjects. The analysis showed 51.79% sensitivity, 100% specificity and 68.86% accuracy. These results are promising but less significant than the one from small world analysis (Vecchio et al 2018).

Currently, network science is developing along a sophistication of network measures and models, introducing new concepts, such as cost-efficiency, hierarchical modularity, vulnerability to random or targeted attack, and the notion of rich clubs.

Transitivity (Tw) is a simple measure of segregation based on the number of triangles in the network. It is computed as the fraction of the node's neighbors that are also neighbors of each other (Watts and Strogatz, 1998) and reflects, on average, the prevalence of clustered connectivity around individual nodes. Tw is a classical variant of Clustering Coefficient not affected by individual node normalization (Newman, 2003). More sophisticated measures of segregation not only describe the presence of densely interconnected groups of regions, but also find the composition of these groups. This composition, known as the network's modular structure (community structure), represents the division of network into groups of nodes, with a maximally possible number of within-group links (within network connections are dense), and a minimally possible number of between-group links (between network connections are sparse). The degree to which the network may be subdivided into such clearly delineated and non-overlapping groups is quantified by a single statistic, the Modularity (Qw). Unlike most other network measures, the optimal modular structure for a given network is typically estimated with optimization algorithms, rather than computed exactly. Finally, Local efficiency (E_{loc}^{w}) is a measure of the efficiency of information transfer limited to neighboring nodes (i.e., nodes with direct edges to the node of interest), and indicates how interconnected neighboring nodes are to each other (Latora and Marchiori, 2001).

The analysis of hierarchical organization of simultaneous oscillations of different frequencies and cross-frequency couplings during a given task performance has opened up opportunities for research into cognitive mechanisms (Buzsaki and Draghun, 2004). Modulation in time of the connectivity pattern of the nodes in a task-related network accounts for much of the variability—i.e. from "excellent" to "poor" performance— of task output in apparently stable conditions of attention and mental concentration (Ferreri et al., 2014; Vecchio et al., 2014a, 2016b). In other words, the task-performance level and the task-related choice/behavior levels are largely written in the immediate architecture of the EEG networks' connectivity, preceding (by a few seconds, usually) the task to be executed.

Each EEG rhythm has a different physiological significance and a complete view—in time, space, and frequency domains—is needed to obtain a comprehensive analysis of the functional dynamics. It is worth mentioning that, depending upon the frequency content of the examined rhythm, the time discrimination of the activation within the network frame can be as short as few msec (down to 10 msec in the high γ band). Because of this, EEG connectivity analysis facilitates an evaluation of the time hierarchy governing the serial/parallel activation of the nodes and their time/space relationship within a given network (i.e. whether A is active before, after, or in parallel to B).

Aging processes modulate the network configuration of brain connectivity. Resting-state EEG characteristics are known to change across physiological aging, with gradual modifications in spectral power profile indicating a pronounced amplitude decrease of α (8–13 Hz) and a global "slowing" of the background EEG, with increases in power and changes in topographic location in the slower δ (2–4 Hz) and θ (4–8 Hz) frequency ranges (Dujardin et al., 1994, 1995; Klass and Brenner, 1995;

Klimesch, 1999; Rossini et al., 2006). Aging processes affect posterior α rhythms, presumably because of the progressive degradation of the activity of dominant oscillatory thalamo-cortical circuits in the resting awake adult brain (Steriade 1998; Brunia, 1999; Pfurtscheller and Lopez da Silva, 1999). They also affect the ability to synchronize in a network organization (Vecchio et al., 2017).

Dementias - particularly in the very early stages - mainly affect synaptic transmission and therefore represent "disconnection syndromes" (Dauwels et al., 2010b; Rossini et al., 2006; Babiloni et al., 2011; Vecchio et al., 2015, 2017). However, a combined use of graph theory to explore brain connectivity from EEG signals and ApoE genotyping as a genetic risk factor for early interception of the "MCI prodromal to AD" condition have been attempted only very recently with highly encouraging results (Vecchio et al, 2018).

Many studies have looked at topographical changes of brain networks with different modalities and have examined structural and diffusion tensor imaging MRI, EEG/MEG and fMRI (see reviews by Xie and He, 2011; Tijms et al., 2013 Neurobiology of Aging). It is worth mentioning that fMRi and EEG connectivity do not reflect exactly the same phenomena; in fact; transient locking/unlocking of neuronal firing as reflected by phase synchronization does not require any energy consumption modification and does not produce any BOLD signal visible in fMRI.

Due to decreasing local and global connectivity parameters, the large-scale functional brain network organization in AD deviates from the optimal small-world architecture towards a more "ordered" type (as reflected by lower SW values), leading to a less efficient information exchange across brain areas in line with the disconnection hypothesis of Alzheimer's Disease (D'Amelio and Rossini, 2012).

A statistically significant difference in the SW organization of those MCI subjects who will progress to AD (Converted= particularly those who can be defined rapid —i.e. 1-2 years— converters) was found; moreover, the Converted aMCI subjects do have SW characteristics very similar to those encountered in Alzheimer patients 1 to 2 years before their conversion (Time 0 of the study, Vecchio et al., 2018). An abnormal increase in graph theory parameters in the Converted, with respect to the Stable MCI, has been observed for the low α rhythm, along with a decrease for the δ and γ rhythms. Such an effect should be interpreted in light of the physiological role the α rhythm. Alpha frequencies constitute the leading characteristic of normal EEG activity at waking rest, which is usually defined as the "idling rhythms" of the adult brain (Niedermeyer and da Silva, 2005). Several studies support the hypothesis that α is a deterministic chaotic signal with several functional correlates –besides others (Stam et al 1999)- ranging from memory formation to sensory-motor processing (Schurmann and Basar, 2001). In healthy individuals, α rhythm does work as an oscillatory component of brain activity and thus can be interpreted as a basic form of information transmission in the brain (Klimesch, 1999). Indeed, event-related activity studies have shown a positive correlation between α frequency and the speed of information processing, as well as a good cognitive performance (Klimesch, 1999). For the δ band, it is argued that, in the awake state, differently from α rhythms which are widely recordable and dominate in the posterior brain areas, δ rhythms are poorly represented, thus reflecting a condition of likely α-δ "reciprocal inhibition" (Rossini et al., 2006). Furthermore, it is well known that the anatomical or functional disconnection of lesioned cortical areas generates spontaneous slow oscillations in the δ range in virtually all recorded neurons. In particular, the SW decrease in the δ band represents a more structured behavior that could be interpreted as an increase of functional inhibition. The opposite holds true for the α band.

A SW decrease in the γ band in the Converted MCI is in line with previous evidence (Vecchio et al., 2014c) showing a decrease of SW γ band in AD with respect to MCI and control subjects. The γ band (>30 Hz) mediates information transfer between cortical and hippocampal structures for memory processes (Vinck et al., 2013), particularly through feed-forward mechanisms (Abeles, 1991) and coherent phase-coupling between oscillations recorded simultaneously from different neuronal structures (Fries, 2005). Both animal and human studies provide evidence that γ oscillations play a fundamental role in memory tasks. Gamma neural activity is involved in numerous cognitive functions, including visual object processing, attention and memory (Tallon-Baudry et al., 1998) and is also strongly associated with behavioral performance (accuracy and reaction time) in several memory tasks, including episodic memory, encoding and retrieval (Kaiser et al., 2008). Further, microelectrodic intraneural recordings demonstrated that γ oscillations are pivotal in spike phase synchronization, which is at the base of EEG connectivity mechanisms (Nikolic et al, 2013).

In a population of 145 MCI subjects followed up for 2 years, the ROC curve showed for EEG SW characteristics with a >60% sensitivity (AUC 0.64, indicating moderate classification accuracy) for classifying the MCI state as a prodromal of AD when all subjects were used. These findings are in line with previous studies (de Haan et al., 2012b; Vecchio et al., 2014c; Miraglia et al., 2016) in which SW characteristics were decreased in low frequency bands in patients with AD compared to MCI (Vecchio et al., 2018). That is, the MCI connectivity pattern was less random than that of the AD group. Moreover, significant differences between healthy elderly, MCI subjects and AD patients have been demonstrated by showing that physiological brain aging presents greater specialization (though lower values) of SW characteristics that are higher than normal in low EEG frequencies and lower in α bands (Vecchio et al., 2016a). Finally, the control analysis, with respect to AD patients, showed that Converted aMCI presented a graph theory pattern practically identical to the AD one. These findings suggest that EEG connectivity analysis, combined with neuropsychological evaluation in MCI, could be of great help in early MCI *prodromal to* AD identification as a first-line screening method and a means to intercept those subjects with a high risk for rapid progression to AD.

It is of paramount interest to consider that the ROC curves showed that, when both phenotype and genotype characteristics (obtained at a low cost with widely available ApoE technology) are combined, the accuracy increased to 91.78 % (AUC 0.97, indicating a nearly optimal classification accuracy) for classifying the MCI state as a prodromal of AD (Vecchio et al 2018). This result is in line with the fact that the ε4 allele of the APOE gene is the major risk genetic factor for pathogenesis of late-onset Alzheimer disease (Huang and Mucke, 2012; Giri et al., 2016).

The intrinsic characteristics of EEG rhythms contain relevant information on early neurodegenerative processes underlying AD. These processes begin long before clinical symptoms manifest, by deranging synaptic transmission and efficacy of brain dynamic connections (D'Amelio and Rossini, 2012). A plastic reorganization of the surviving neuronal circuitries -the neural "reserve"- contrasts such a neurodegenerative attack nulling or limiting the impact on daily living abilities. This is explaining the prolonged presymptomatic period (Rossini et al., 2006; D'Amelio and Rossini, 2012; Ferreri et al., 2003). In aMCI-C subjects, the SW characteristics provided reliable predictions of aMCI to AD progression within a relatively short timeframe. Moreover, rapid progression from aMCI to AD heralds an aggressive type of dementia with a rapid degradation of daily life skills.

8. Toward automated EEG-based Alzheimer's disease diagnosis?

Alzheimer's disease (AD) diagnostic accuracy rate by experienced clinicians varies from 80 to 90% and requires a huge amount of resources, from high-tech equipment to highly trained experts that are primarily found only at medical centers in developed countries (Sarazin et al., 2012).
Consequently, non-invasive, low-cost and straightforward automated techniques for early AD diagnosis should be developed and improved. A promising candidate to achieve this goal is neural signal analysis through quantitative electroencephalography (qEEG).
Notwithstanding, in order to develop a fully automated system to support clinicians in AD diagnosis, further improvements in qEEG algorithms are required regarding artifact removal techniques, feature extraction, feature selection and automatic classification strategies. The schematics of an ideal automated EEG-based system for early diagnosis of AD (leave-one-subject-out training paradigm) is depicted in Fig. 3 (Cassani et al., 2014). Herein we will make a quick review on state-of-the art algorithms related to each of these system components. So far the great majority of studies in EEG-based biomarkers for AD early diagnosis rely on the resting-awake experimental protocol, thus for the sake of compactness we will restrict our review to this approach As previously described, four main effects on EEG signals from Alzheimer's patients have been recurrently observed: slowing, reduced complexity, decreased synchrony, neuromodulatory deficit in EEG rhythms and loss of frequency-dependent connectivity. As for the former three effects, a comprehensively review was performed (Dauwels et al., 2010a). For connectivity analysis the Reader is referred to the related section of this manuscript. Regarding the quantification of the neuromodulatory activity, amplitude modulation analysis was propositioned as a spectral-temporal technique, allowing direct characterization of cross-frequency interaction effects by measuring the rates at which EEG bands are modulated (Falk et al., 2012; Fraga et al., 2013). The procedure of feature averaging is an interesting additional tool proven to improve the accuracy in AD diagnosis (Fraga et al., 2013). This step is similar to the epoch averaging commonly performed in event-related potential studies, but differs in the sense that it runs in the (non-linear) feature domain rather than in the time domain.
The combination of all the above-mentioned feature extraction techniques results in a wide-ranging collection of features. For this reason, a feature selection process necessarily should be done in an automated or at least in a semi-automated way. A large number of machine learning algorithms can be used to accomplish this task. A widely used procedure for both feature selection and classification in diagnosing AD applications is support vector machine (SVM), which achieved up to 98% accuracy in early AD detection (Falk et al., 2012; Fraga et al., 2013; Trambaiolli et al., 2011). One of the major advantages of SVM is that, using it together with the L1-norm as penalization, it leads to sparse weight vectors and allows feature selection and classification to be accomplished in the same step (Cassani et al., 2017). An interesting variation of SVM is the Relevance Vector Machine (RVM), which replaces the binary SVM classifier with a soft-decision method based on a probabilistic Bayesian learning framework and outperformed SVM when tested in a fully-automated AD diagnostic system (Cassani et al., 2014).

9. Conclusions

In this manuscript it was attempted an integrated and interdisciplinary approach to the "early" diagnosis of Alzheimer disease with the idea to move from the concept of early identification of *Mild*

Cognitive Impairment prodromal to AD to the systematic screening of at risk populations in view of the possible arrival of disease-modifying drugs.

During a meeting held in Rome in June 2017 a panel of Experts from different disciplines has discussed this problem integrating the various disciplines involved in this field (epidemiology, neuropsychology, fluid testing, genetics, neuroimaging both structural and functional, EEG/MEG both spontaneous and task-related). Many of them agreed to prepare a common manuscript providing a review of the strengths and weaknesses of the individual biomarkers for early diagnosis. The International Federation of Clinical Neurophysiology has supported this meeting; such an endorsement has been triggered by the "vision" that the neurophysiological methods (in particular the advanced analysis of electromagnetic brain signals) could represent a first-line screening tool particularly for their for their high sensitivity to synaptic function, non-invasiveness, low-cost and widespread availability. Since EEG/MEG digitized signals can be easily translated via a technological platform from recording places on the territory to expert's centers for sophisticated analysis, harmonization of the analysis methods can be and should be accomplished. Needless to say, neurophysiological methods alone cannot reach neither the required accuracy nor the diagnostic specificity (i.e. distinguish AD from other dementias or amyloid-positive from amyloid-negative AD forms), but –if combined with other biomarkers with the same characteristics (innocuous, low-cost, widely available)- could contribute for a first-line screening that allows for defining high-risk subjects currently investigated only with highly sophisticated/expensive (i.e. volumetric MRI, PET with radioligands) and invasive (i.e. lumbar puncture) approaches. Given 100% cases on entry, one could predict to remain with about 15-20% cases for second- and third-line further evaluation, making the whole scenario affordable both from the organizational and financial sides. The literature review presented here indicates several approaches that are extremely promising to open a new era in EEG/MEG methods to innovative clinical applications in the field of dementia eraly diagnosis with huge implications. Companies are very slow in appreciating this opportunity, while researchers from the neuroscientific clinical community seem to be -once again- on the frontline.

Let's go on and try to realize this dream!

References

- Abásolo D, Escudero J, Hornero R, Gómez C, Espino P. Approximate entropy and auto mutual information analysis of the electroencephalogram in Alzheimer's disease patients. Med Biol Eng Comput 2008; 46:1019-1028.
- Abásolo D, Hornero R, Espino P, Álvarez D, Poza J. Entropy analysis of EEG background activity in Alzheimer's disease patients. Physiol Meas 2006a; 27:241-253.
- Abásolo D, Hornero R, Gómez C, García M, López M. Analysis of EEG background activity in Alzheimer's disease patients with Lempel-Ziv complexity and central tendency measure. Med Eng Phys 2006b; 28:315-322.
- Abeles M. Corticonics: neural circuits of the cerebral cortex. New York: Cambridge UP, 1991.
- Adler G, Brassen S, Jajcevic A. EEG coherence in Alzheimer's dementia. J Neural Transm 2003; 110:1051-1058.
- Adrian ED, Moruzzi, G. Impulses in the pyramidal tract. J Physiol 1939; 97:153-99.
- Ahmed MU, Mandic DP. Multivariate multiscale entropy: A tool for complexity analysis of multichannel data. Phys Rev E 2011; 84:61918.

- Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7:270-9.
- Aoki Y, Ishii R, Pascual-Marqui RD, Canuet L, Ikeda S, Hata M et al. Detection of EEG-resting state independent networks by eLORETA-ICA method. Front Hum Neurosci 2015; 9:31.
- Arevalo-Rodriguez I, Smailagic N, Roqué I Figuls M, Ciapponi A, Sanchez-Perez E, et al. Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 2015; 3:CD010783.
- Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage 2000; 11:805-21.
- Azami H, Abásolo D, Simons S, Escudero J. Univariate and Multivariate Generalized Multiscale Entropy to Characterise EEG Signals in Alzheimer's Disease. Entropy 2017a; 19:31.
- Azami H, Escudero J. Amplitude- and Fluctuation-Based Dispersion Entropy. Entropy 2018a [In press].
- Azami H, Escudero J. Coarse-Graining Approaches in Univariate and Multiscale Sample and Dispersion Entropy. Entropy 2018b; 20:138.
- Azami H, Escudero J. Refined composite multivariate generalized multiscale fuzzy entropy: A tool for complexity analysis of multichannel signals. Phys A 2017; 465:261-276.
- Azami H, Rostaghi M, Abásolo D, Escudero J. Refined Composite Multiscale Dispersion Entropy and its Application to Biomedical Signals. IEEE Trans Biomed Eng 2017b; 64:2872-2879.
- Babiloni C, Babiloni F, Carducci F, Cincotti F, Del Percio C, De Pino G, et al. Movement-related electroencephalographic reactivity in Alzheimer Disease. Neuroimage 2000; 12:139-46.
- Babiloni C, Benussi L, Binetti G, Bosco P, Busonero G, Cesaretti S, et al. Genotype (cystatin C) and EEG phenotype in Alzheimer disease and mild cognitive impairment: a multicentric study. Neuroimage 2006a; 29:948-64.
- Babiloni C, Benussi L, Binetti G, Cassetta E, Dal Forno G, Del Percio C, et al. Apolipoprotein E and α brain rhythms in mild cognitive impairment: a multicentric electroencephalogram study. Ann Neurol 2006b; 59:323-34.
- Babiloni C, Binetti G, Cassetta E, Cerboneschi D, Dal Forno G, Del Percio C, et al. Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. A multicentric EEG study. Neuroimage 2004; 22:57-67.
- Babiloni C, Bosco P, Ghidoni R, Del Percio C, Squitti R, Binetti G, et al. Homocysteine and electroencephalographic rhythms in Alzheimer disease: a multicentric study. Neuroscience 2007; 145:942-54.
- Babiloni C, Carducci F, Lizio R, Vecchio F, Baglieri A, Bernardini S, et al. Resting state cortical electroencephalographic rhythms are related to gray matter volume in subjects with mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp 2013; 34:1427-46.
- Babiloni C, Cassetta E, Chiovenda P, Del Percio C, Ercolani M, Moretti DV, et al. A rhythms in mild dements during visual delayed choice reaction time tasks: a MEG study. Brain Res Bull 2005; 65:457-70.
- Babiloni C, De Pandis MF, Vecchio F, Buffo P, Sorpresi F, Frisoni GB, et al. Cortical sources of resting state electroencephalographic rhythms in Parkinson's disease related dementia and Alzheimer's disease. Clin Neurophysiol 2011; 122:2355-64.
- Babiloni C, Del Percio C, Boccardi M, Lizio R, Lopez S, Carducci F, et al. Occipital sources of resting-state α rhythms are related to local gray matter density in subjects with amnesic mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2015; 36:556-70.
- Babiloni C, Del Percio C, Caroli A, Salvatore E, Nicolai E, Marzano N, et al. Cortical sources of resting state EEG rhythms are related to brain hypometabolism in subjects with Alzheimer's disease: an EEG-PET study. Neurobiol Aging 2016b; 48:122-134.
- Babiloni C, Del Percio C, Vecchio F, Sebastiano F, Di Gennaro G, Quarato PP, et al. A, β and γ electrocorticographic rhythms in somatosensory, motor, premotor and prefrontal cortical areas differ in movement execution and observation in humans. Clin Neurophysiol 2016c; 127:641-654.
- Babiloni C, Frisoni GB, Pievani M, Vecchio F, Lizio R, Buttiglione M, et al. Hippocampal volume and cortical sources of EEG α rhythms in mild cognitive impairment and Alzheimer disease. Neuroimage 2009; 44:123-35.
- Babiloni C, Lizio R, Marzano N, Capotosto P, Soricelli A, Triggiani AI, et al. Brain neural synchronization and functional coupling in Alzheimer's disease as revealed by resting state EEG rhythms. Int J Psychophysiol 2016a; 103:88-102.
- Babiloni C, Lizio R, Vecchio F, Frisoni GB, Pievani M, Geroldi C, et al. Reactivity of cortical α rhythms to eye opening in mild cognitive impairment and Alzheimer's disease: an EEG study. J Alzheimers Dis 2010a; 22:1047-64.
- Babiloni C, Vecchio F, Lizio R, Ferri R, Rodriguez G, Marzano N, et al. Resting state cortical rhythms in mild cognitive impairment and Alzheimer's disease: electroencephalographic evidence. J Alzheimers Dis 2011; 3:201-214.
- Babiloni C, Visser PJ, Frisoni G, De Deyn PP, Bresciani L, Jelic V, et al. Cortical sources of resting EEG rhythms in mild cognitive impairment and subjective memory complaint. Neurobiol Aging 2010b; 31:1787-98.
- Babiloni F, Cincotti F, Carducci F, Rossini PM, Babiloni C. Spatial enhancement of EEG data by surface Laplacian estimation: the use of magnetic resonance imaging-based head models. Clin Neurophysiol 2001; 112:724-7.
- Bandt C, Pompe B. Permutation Entropy: A Natural Complexity Measure for Time Series. Phys Rev Lett 2002; 88:174102.

- Barbati G, Porcaro C, Zappasodi F, Rossini PM, Tecchio F. Optimization of ICA approach for artifact identification and removal in MEG signals. Clin Neurophysiol 2004; 115:1220-32.
- Barnett JH, Lewis L, Blackwell AD, Taylor M. Early intervention in Alzheimer's disease: a health economic study of the effects of diagnostic timing. BMC Neurol 2014; 14:101.
- Barry RJ, De Blasio FM, Borchard JP. Sequential processing in the equiprobable auditory Go/NoGo task: children vs. adults. Clin Neurophysiol 2014; 125:1995-2006.
- Başar E, Başar-Eroğlu C, Karakaş S, Schürmann M. Γ, α,δ, and thet aoscillations govern cognitive processes. Int J Psychophysiol 2001; 39: 241-248.
- Başar E, Emek-Savaş DD, Güntekin B, Yener GG. Delay of cognitive γ responses in Alzheimer's disease. Neuroimage Clin 2016; 11:106-15.
- Başar E, Güntekin B. A short review of α activity in cognitive processes and in cognitive impairment. Int J Psychophysiol 2012; 86:25-38.
- Başar E, Tülay E, Güntekin B. Multiple γ oscillations in the brain: A new strategy to differentiate functional correlates and P300 dynamics. Int J Psychophysiol 2015; 95:406-420.
- Başar E. A review of α activity in integrative brain function: fundamental physiology, sensory coding, cognition and pathology. Int J Psychophysiol 2012; 86:1-24.
- Başar E. A review of γ oscillations in healthy subjects and in cognitive impairment. Int J Psychophysiol 2013; 90:99-117.
- Başar E. Brain Function and Oscillations. I. Brain Oscillations: Principles and Approaches. Springer, Berlin, Heidelberg, 1998.
- Başar E. Brain function and oscillations. II. Integrative brain function. Neurophysiology and Cognitive Processes. Springer, Berlin, Heidelberg, 1999.
- Başar E. EEG–Brain Dynamics. Relation between EEG and Brain Evoked Potentials. Elsevier, Amsterdam, 1980.
- Başar-Eroglu C, Strüber D, Schürmann M, Stadler M, Başar E. Γ-band responses in the brain: a short review of psychophysiological correlates and functional significance. Int J Psychophysiol 1996; 24:101-112.
- Basser PJ, Jones DK. Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. NMR Biomed 2002; 15:456-67.
- Bassett DS, Bullmore E. Small-world brain networks. Neuroscientist 2006; 12:512-523.
- Bennett DA, Wilson RS, Boyle PA, Buchman AS, Schneider JA. Relation of neuropathology to cognition in persons without cognitive impairment. Ann Neurol 2012; 72:599-609.
- Bertram L, Tanzi RE. Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. Nat Rev Neurosci 2008; 9:768-78.
- Besthorn C, Sattel H, Geiger-Kabisch C, Zerfass R, Förstl H. Parameters of EEG dimensional complexity in Alzheimer's disease. Electroencephalogr Clin Neurophysiol 1995; 95:84-9.
- Blanco S, Garcia H, Quiroga RQ, Romanelli L, Rosso OA. Stationarity of the EEG Series. IEEE Eng Med Biol 1995; 14:395-399.
- Boccaletti S, Valladares DL, Pecora LM, Geffert HP, Carroll T. Reconstructing embedding spaces of coupled dynamical systems from multivariate data. Phys Rev E Stat Nonlin Soft Matter Phys 2002; 65:035204.
- Bohnen NI, Djang DS, Herholz K, Anzai Y, Minoshima S. Effectiveness and safety of 18F-FDG PET in the evaluation of dementia: a review of the recent literature. J Nucl Med 2012; 53:59-71.
- Boyle PA, Wilson RS, Yu L, Barr AM, Honer WG, Schneider JA, et al. Much of late life cognitive decline is not due to common neurodegenerative pathologies. Ann Neurol 2013; 74:478-89.
- Bozzali M, Dowling C, Serra L, Spanò B, Torso M, Marra C, et al. The impact of cognitive reserve on brain functional connectivity in Alzheimer's disease. J Alzheimers Dis 2015; 44:243-50.
- Bozzali M, Filippi M, Magnani G, Cercignani M, Franceschi M, Schiatti E, et al. The contribution of voxel-based morphometry in staging patients with mild cognitive impairment. Neurology 2006; 67:453-60.
- Bozzali M, Giulietti G, Basile B, Serra L, Spanò B, Perri R, et al. Damage to the cingulum contributes to Alzheimer's disease pathophysiology by deafferentation mechanism. Hum Brain Mapp 2012; 33:1295-308.
- Bozzali M, Parker GJ, Serra L, Embleton K, Gili T, Perri R, et al. Anatomical connectivity mapping: a new tool to assess brain disconnection in Alzheimer's disease. Neuroimage 2011; 54:2045-51.
- Bozzali M, Parker GJ, Spanò B, Serra L, Giulietti G, Perri R, et al. Brain tissue modifications induced by cholinergic therapy in Alzheimer's disease. Hum Brain Mapp 2013; 34:3158-67.
- Bozzali M, Serra L, Cercignani M. Quantitative MRI to understand Alzheimer's disease pathophysiology. Curr Opin Neurol 2016; 29:437-44.
- Breakspear M. Dynamic models of large-scale brain activity. Nat Neurosci 2017; 20:340-352.
- Breitner JCS, Wyse BW, Anthony JC. APOE-ε4 count predicts age when prevalence of AD increases, then declines. The Cache County Study. Neurology 1999; 53:321.
- Bruni AC, Bernardi L, Colao R, Rubino E, Smirne N, Frangipane F, et al. Worldwide distribution of PSEN1 Met146Leu mutation: a large variability for a founder mutation. Neurology 2010; 74:798-806.

- Brunia CH. Neural aspects of anticipatory behavior. Neural aspects of anticipatory behavior. Acta Psychol (Amst) 1999; 101:213-42.
- Buchman AS, Yu L, Wilson RS, Boyle PA, Schneider JA, Bennett DA. Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. J Gerontol A Biol Sci Med Sci 2014; 69:1536-44.
- Buzsaki G, Christen Y. Micro-, Meso- and Macro-Dynamics of the Brain. Editors Buzsáki G and Christen Y, Cham (CH), Spinger 2016.
- Buzsaki G, Draguhn A. Neuronal oscillations in cortical networks. Science 2004; 304:1926-9.
- Buzsaki G, Schomburg EW. What does γ coherence tell us about inter-regional neural communication? Nat Neurosci 2015; 18:484-9.
- Buzsaki G. Neuroscience: neurons and navigation. Nature 2005; 436:781-2.
- Canuet L, Ishii R, Pascual-Marqui RD, Iwase M, Kurimoto R, Aoki Y et al. Resting-state EEG source localization and functional connectivity in schizophrenia-like psychosis of epilepsy. PLoS One 2011; 6:e27863.
- Canuet L, Tellado I, Couceiro V, Fraile C, Fernandez-Novoa L, Ishii R, et al. Resting-state network disruption and APOE genotype in Alzheimer's disease: a lagged functional connectivity study. PLoS One 2012; 7:e46289.
- Cao C, Slobounov S. Alteration of cortical functional connectivity as a result of traumatic brain injury revealed by graph theory, ICA, and sLORETA analyses of EEG signals. EEE Trans Neural Syst Rehabil Eng 2010; 18:11-9.
- Cao Y, Cai L, Wang J, Wang R, Yu H, Cao Y, et al. Characterization of complexity in the electroencephalograph activity of Alzheimer's disease based on fuzzy entropy. Chaos Interdiscip J Nonlinear Sci 2015; 25:83116.
- Caravaglios G, Castro G, Costanzo E, Di Maria G, Mancuso D, Muscoso EG. Θ power responses in mild Alzheimer's disease during an auditory oddball paradigm:lack of θ enhancement during stimulus processing. J Neural Transm 2010; 117:1195-1208.
- Caravaglios G, Costanzo E, Palermo F, Muscoso EG. Decreased amplitude of auditory event-related δ responses in Alzheimer's disease. Int J Psychophysiol 2008; 70:23-32.
- Cassani R, Falk TH, Fraga FJ, Cecchi M, Moore DK, Anghinah R. Towards automated electroencephalography-based Alzheimer ' s disease diagnosis using portable low-density devices. Biomed Signal Process Control 2017; 33: 261-271.
- Cassani R, Falk TH, Fraga FJ, Kanda PAM, Anghinah R. The effects of automated artifact removal algorithms on electroencephalography-based Alzheimer's disease diagnosis. Front Aging Neurosci 2014; 6:55.
- Catricalà E, Gobbi E, Battista P, Miozzo A, Polito C, Boschi V, et al. SAND: a Screening for Aphasia in NeuroDegeneration. Development and normative data. Neurol Sci 2017; 38:1469-1483.
- Cerami C, Dubois B, Boccardi M, Monsch A, Demonet J, Cappa S. The Geneva Task Force for the Roadmap of Alzheimer's Biomarkers, Clinical validity of delayed recall tests as a gateway-biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. Neurobiol Aging 2017; 52:153-166.
- Chaumon M, Bishop DVM, Busch NA. A practical guide to the selection of independent components of the electroencephalogram for artifact correction. J. Neurosci Methods 2015; 250:47-63.
- Chen W, Wang Z, Xie H, Yu W. Characterization of Surface EMG Signal Based on Fuzzy Entropy. IEEE Trans Neural Syst Rehabil Eng 2007; 15:266-272.
- Cheng ST. Dementia Caregiver Burden: a Research Update and Critical Analysis. Curr Psychiatry Rep 2017; 19:64.
- Ciesla M, Skrzypek K, Kozakowska M, Loboda A, Jozkowicz A, Dulak J. MicroRNAs as biomarkers of disease onset. Anal Bioanal Chem 2011; 401:2051-61.
- Cohen AD, Rabinovici GD, Mathis CA, Jagust WJ, Klunk WE, Ikonomovic MD. Using Pittsburgh Compound B for in vivo PET imaging of fibrillar amyloid-β. Adv Pharmacol 2012; 64:27-81.
- Colangeli S, Boccia M, Verde P, Guariglia P, Bianchini F, Piccardi L. Cognitive Reserve in Healthy Aging and Alzheimer's Disease: A Meta-Analysis of fMRI Studies. Am J Alzheimers Dis Other Dement 2016; 31:443-9.
- Conidi ME, Bernardi L, Puccio G, Smirne N, Muraca MG, Curcio SA, et al. Homozygous carriers of APP A713T mutation in an autosomal dominant Alzheimer disease family. Neurology 2015; 84:2266-73.
- Coronel C, Garn H, Waser M, Deistler M, Benke T, Dal-Bianco P, et al. Quantitative EEG Markers of Entropy and Auto Mutual Information in Relation to MMSE Scores of Probable Alzheimer's Disease Patients. Entropy 2017; 19:130.
- Costa A, Bak T, Caffarra P, Caltagirone C, Ceccaldi M, Collette F, et al. The need for harmonisation and innovation of neuropsychological assessment in neurodegenerative dementias in Europe: consensus document of the Joint Program for Neurodegenerative Diseases Working Group. Alzheimers Res Ther 2017; 9:27.
- Costa M, Goldberger AL, Peng CK. Multiscale entropy analysis of biological signals. Phys Rev E Stat Nonlin Soft Matter Phys 2005; 71:21906.
- Courtiol J, Perdikis D, Petkoski S, Müller V, Huys R, Sleimen-Malkoun R, et al. The multiscale entropy: Guidelines for use and interpretation in brain signal analysis. J Neurosci Methods 2016; 273:175-190.
- Crutch SJ, Schott JM, Rabinovici GD, Murray M, Snowden JS, van der Flier WM, et al. Consensus classification of posterior cortical atrophy. Alzheimers Dement 2017; 13:870-884.
- Cummings JL, Mega M, Gray K, Rosemberg-Thompson S, Carusi DA, Gornbei J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44:2308-2314.

- Cummings JL, Miller BL, Christensen DD, Cherry D. Creativity and dementia: emerging diagnostic and treatment methods for Alzheimer's disease. CNS Spectr 2008; 13:1-20.
- Cummins TD, Broughton M, Finnigan S. Θ oscillations are affected by amnestic mild cognitive impairment and cognitive load. Int J Psychophysiol 2008; 70:75-81.
- D'Amelio M, Rossini PM. Brain excitability and connectivity of neuronal assemblies in Alzheimer's disease: from animal models to human findings. Prog Neurobiol 2012; 99:42-60.
- Dauwels J, Vialatte F, Cichocki A. Diagnosis of Alzheimer's disease from EEG signals: where are we standing? Curr Alzheimer Res 2010a; 7:487-505.
- Dauwels J, Vialatte F, Musha T, Cichocki A. A comparative study of synchrony measures for the early diagnosis of Alzheimer's disease based on EEG Neuroimage 2010b; 49:668-693.
- de Haan W, Mott K, van Straaten EC, Scheltens P, Stam JC. Activity dependent degeneration explains hub vulnerability in Alzheimer's disease. PLoS Comput Biol 2012a; 8:e1002582.
- de Haan W, Pijnenburg YA, Strijers RL, van der Made Y, van der Flier WM, Scheltens P et al. Functional neural network analysis in frontotemporal dementia and Alzheimer's disease using EEG and graph theory. BMC Neurosci 2009; 10:101.
- de Haan W, van der Flier WM, Koene T, Smits LL, Scheltens P, Stam CJ. Disrupted modular brain dynamics reflect cognitive dysfunction in Alzheimer's disease. Neuroimage 2012b; 59:3085-3093.
- Deiber M, Iba V, Missonnier P. Abnormal-induced θ activity supports early directed-attention network deficits in progressive MCI. Neurobiol Aging 2009; 30:1444-52.
- Deiber MP, Meziane HB, Hasler R, Rodriguez C, Toma S, Ackermann M, et al. Attention and Working Memory-Related EEG Markers of Subtle Cognitive Deterioration in Healthy Elderly Individuals. J Alzheimers Dis 2015; 47:335-49.
- Del Gratta C, Pizzella V, Tecchio F, Romani GL. Magnetoencephalography-a noninvasive brain imaging method with 1 ms time resolution. Reports Prog Phys 2001; 64:12.
- Delorme A, Makeig S. EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004; 134:9-21.
- Delorme A, Sejnowski T, Makeig S. Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. Neuroimage 2007; 34:1443-1449.
- Deng B, Cai L, Li S, Wang R, Yu H, Chen Y, et al. Multivariate multi-scale weighted permutation entropy analysis of EEG complexity for Alzheimer's disease. Cogn Neurodyn 2017; 11:217-231.
- Deng B, Liang L, Li S, Wang R, Yu H, Wang J, et al. Complexity extraction of electroencephalograms in Alzheimer's disease with weighted-permutation entropy. Chaos Interdiscip J Nonlinear Sci 2015; 25:43105.
- Dierckx E, Engelborghs S, De Raedt R, Van Buggenhout M, De Deyn P, Verté D, et al. Verbal cued recall as a predictor of conversion to Alzheimer's disease in Mild Cognitive Impairment. Int J Geriatr Psychiatry 2009; 24:1094-1100.
- Dierks T, Ihl R, Frölich L, Maurer K. Dementia of the Alzheimer type: effects on the spontaneous EEG described by dipole sources. Psychiatry Res 1993; 50:151-62.
- Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010; 9:1118-1127.
- Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007; 6:734-746.
- Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. The Lancet Neurology 2014; 13:614-629.
- Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement 2016; 12:292-323.
- Dubois B, Touchon J, Portet F, Ousset P, Vellas B, Michel B. " The 5 words": a simple and sensitive test for the diagnosis of Alzheimer's disease. Presse Med 2002; 31:1696-1699.
- Dujardin K, Bourriez JL, Guieu JD. Event-related desynchronization (ERD) patterns during verbal memory tasks: effect of age. Int J Psychophysiol 1994; 16:17-27.
- Dujardin K, Bourriez JL, Guieu JD. Event-related desynchronization (ERD) patterns during memory processes: effects of aging and task difficulty. Electroencephalogr Clin Neurophysiol 1995; 96:169-82.
- Economou A, Routsis C, Papageorgiou SG. Episodic memory in Alzheimer disease, frontotemporal dementia, and dementia with Lewy bodies/Parkinson disease dementia: disentangling retrieval from consolidation. Alzheimer Dis Assoc Disord 2016; 30:47-52.
- Engel AK, Fries P. B-band oscillations--signalling the status quo? Curr Opin Neurobiol 2010; 20:156-65.
- Epelbaum S, Genthon R, Cavedo E, Habert MO, Lamari F, Gagliardi G, et al. Preclinical Alzheimer's disease: A systematic review of the cohorts underlying the concept. Alzheimers Dement 2017; 13:454-467.
- Escudero J, Abasolo D, Hornero R, Espino P, Lopez M. Analysis of electroencephalograms in Alzheimer's disease patients with multiscale entropy. Physiol Meas 2006; 27:1091-1106.
- Escudero J, Ibanez-Molina A, Iglesias-Parro S. Effect of the average delay and mean connectivity of the Kuramoto model on the complexity of the output electroencephalograms. Conf Proc IEEE Eng Med Biol Soc 2015; 2015:7873-6.

- Esteller R, Vachtsevanos G, Echauz J, Litt B. A comparison of waveform fractal dimension algorithms. IEEE Trans Circuits Syst Fundam Theory Appl 2011; 48:177-183.
- Faes L, Porta A, Nollo G. Information Decomposition in Bivariate Systems: Theory and Application to Cardiorespiratory Dynamics. Entropy 2015; 17:277-303.
- Falk TH, Fraga FJ, Trambaiolli L, Anghinah R. Open Access EEG amplitude modulation analysis for semi-automated diagnosis of Alzheimer 's disease. J Adv Signal Process 2012; 2012:192.
- Fazekas F, Chawluk JB, Alvavi A. Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5T in Alzheimer's disease and normal aging. AJR Am J Roentgenol 1987; 149:351-6.
- Fei M, Jianhua W. Apolipoprotein ε4-allele as a significant risk factor for conversion from mild cognitive impairment to Alzheimer's disease: a meta-analysis of prospective studies. J Mol Neurosci 2013; 50:257-63.
- Ferreri F, Pauri F, Pasqualetti P, Fini R, Dal Forno G, Rossini PM. Motor cortex excitability in Alzheimer's disease: a transcranial magnetic stimulation study. Ann Neurol 2003; 53:102-108.
- Ferreri F, Vecchio F, Ponzo D, Pasqualetti P, Rossini PM. Time-varying coupling of EEG oscillations predicts excitability fluctuations in the primary motor cortex as reflected by motor evoked potentials amplitude: An EEG-TMS study. Hum Brain Mapp 2014; 35:1969-80.
- Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005; 366:2112-7.
- Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ. Paired associate performance in the early detection of DAT. J Int Neuropsychol Soc 2002; 8:58-71.
- Fraga FJ, Falk TH, Trambaiolli LR, Oliveira EF, Walter HL, Federal U, et al. Towards an EEG-based biomarker for Alzheimer's disease: Improving amplitude modulation analysis features. Proc IEEE Int Conf Acoust Speech Signal Process 2013; 1207-1211.
- Fraga FJ, Ferreira LA, Falk TH, Johns E, Phillips ND. Event-related synchronisation responses to N-back memory tasks discriminate between healthy ageing, mild cognitive impairment, and mild Alzheimer's disease. Proc IEEE Int Conf Acoust Speech Signal Process 2017; 964-8.
- Frasson P, Ghiretti R, Catricalà E, Pomati S, Marcone A, Parisi L, et al. Free and cued selective reminding test: an Italian normative study. Neurol Sci 2011; 32:1057-1062.
- Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence, Trends Cogn Sci 2005; 9:474-480.
- Frisoni GB, Bocchetta M, Chételat G, Rabinovici GD, de Leon MJ, Kaye J, et al. ISTAART's NeuroImaging Professional Interest Area. Imaging markers for Alzheimer's disease: which vs how. Neurology 2013; 81:487-500.
- Fuentemilla L, Marco-Pallarés J, Grau C. Modulation of spectral power and of phase resetting of EEG contributes differentially to the generation of auditory event-related potentials. Neuroimage 2006; 30:909-16.
- Garn H, Waser M, Deistler M, Benke T, Dal-Bianco P, Ransmayr G, et al. Quantitative EEG markers relate to Alzheimer's disease severity in the Prospective Dementia Registry Austria (PRODEM). Clin Neurophysiol 2015; 126:505-513.
- Garrard P, Ahmed S. An abbreviated examination for the assessment of linguistic impairment in primary progressive aphasia. Eur J Neurol 2012; 19:561.
- Geldmacher DS. Cost-effectiveness of drug therapies for Alzheimer's disease: A brief review. Neuropsychiatr Dis Treat 2008; 4:549-55.
- Getsios D, Blume S, Ishak KJ, Maclaine G, Hernández L. An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. Alzheimers Dement 2012; 8:22-30.
- Gevins A, Smith ME, McEvoy L, Yu D. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. Cereb Cortex 1997; 7:374-385.
- Gevins A, Smith ME. Neurophysiological measures of working memory and individual differences in cognitive ability and cognitive style. Cereb Cortex 2000; 10:829-839.
- Giannakopoulos P, Missonnier P, Kövari E, Gold G, Michon A. Electrophysiological markers of rapid cognitive decline in mild cognitive impairment. Front Neurol Neurosci 2009; 24:39-46.
- Gianotti LR, Künig G, Lehmann D, Faber PL, Pascual-Marqui RD, Kochi K, et al. Correlation between disease severity and brain electric LORETA tomography in Alzheimer's disease. Clin Neurophysiol 2007; 118:186-96.
- Gili T, Cercignani M, Serra L, Perri R, Giove F, Maraviglia B, et al. Regional brain atrophy and functional disconnection across Alzheimer's disease evolution. J Neurol Neurosurg Psychiatry 2011; 82:58-66.
- Giri M, Zhang M, Lu Y. Genes associated with Alzheimer's disease: an overview and current status. Clin Interv Aging 2016; 11:665-681.
- Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 1991; 349:704-706.
- Golby A, Silverberg G, Race E, Gabrieli S, O'Shea J, Knierim K, et al. Memory encoding in Alzheimer's disease: an fMRI study of explicit and implicit memory. Brain 2005; 128:773-87.

- Goldberger AL, Amaral LAN, Hausdorff JM, Ivanov PC, Peng CK, Stanley HE. Fractal dynamics in physiology: Alterations with disease and aging. Proc Natl Acad Sci USA 2002; 99:2466-2472.
- Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa S, et al. Classification of primary progressive aphasia and its variants. Neurology 2011; 76:1006-1014.
- Gramfort A, Luessi M, Larson E, Engemann DA, Strohmeier D, Brodbeck C, et al. MEG and EEG data analysis with MNE-Python. Front Neurosci 2013; 7:267.
- Grande G, Vanacore N, Vetrano DL, Cova, I, Rizzuto D, Mayer F, et al. Free and Cued Selective Reminding Test predicts progression to Alzheimer's disease in people with Mild Cognitive Impairment [Unpublished results]
- Grassberger P, Procaccia I. Measuring the strangeness of strange attractors. Phys Nonlinear Phenom 1983; 9:189-208.
- Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 2003; 100:253-8.
- Grober E, Buschke H. Genuine memory deficits in dementia. Dev Neuropsychol 1987; 3:13-36.
- Güntekin B, Başar E. A review of brain oscillations in perception of faces and emotional pictures. Neuropsychologia 2014; 58:33-51.
- Güntekin B, Başar E. Review of evoked and event-related δ responses in the human brain. Int J Psychophysiol 2016; 103:43-52.
- Güntekin B, Emek-Savaş DD, Kurt P, Yener GG, Başar E. B oscillatory responses in healthy subjects and subjects with mild cognitive impairment. Neuroimage Clin 2013; 3:39-46.
- Hämäläinen MS, Ilmoniemi RJ. Interpreting magnetic fields of the brain: minimum norm estimates. Med Biol Eng Comput 1994; 32:35-42.
- Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002; 297:353-6.
- Heaton RK, Chelune GJ, Talley JL, Grant DA, Berg EA. Wisconsin card sorting test: revised and expanded. Psychological Assessment Resources (PAR), 1993.
- Henderson G, Ifeachor E, Hudson N, Goh C, Outram N, Wimalaratna S, et al. Development and assessment of methods for detecting dementia using the human electroencephalogram. IEEE Trans Biomed Eng 2006; 53:1557-1568.
- Herholz K, Westwood S, Haense C, Dunn G. Evaluation of a calibrated (18)F-FDG PET score as a biomarker for progression in Alzheimer disease and mild cognitive impairment. J Nucl Med 2011; 52:1218-26.
- Herrmann CS, Munk MH, Engel AK. Cognitive functions of γ-band activity:memory match and utilization. Trends Cogn Sci 2004; 8:347-355.
- Higuchi T. Approach to an irregular time series on the basis of the fractal theory. Phys Nonlinear Phenom 1988; 31:277-283.
- Hjorth B. Principles for transformation of scalp EEG from potential field into source distribution. J Clin Neurophysiol 1991; 8:391-396.
- Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, et al. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. CMAJ 2008; 179:1019-26.
- Hornero R, Abásolo D, Escudero J, Gómez C. Nonlinear analysis of electroencephalogram and magnetoencephalogram recordings in patients with Alzheimer's disease. Philos Trans R Soc Math Phys Eng Sci 2009; 367: 317-336.
- Hornero R, Escudero J, Fernandez A, Poza J, Gomez C. Spectral and Nonlinear Analyses of MEG Background Activity in Patients With Alzheimer's Disease. IEEE Trans Biomed Eng 2008; 55:1658-1665.
- Hsiao FJ, Wang YJ, Yan SH, Chen WT, Lin YY. Altered oscillation and synchronization of default-mode network activity in mild Alzheimer's disease compared to mild cognitive impairment: an electrophysiological study. PLoS One 2013; 8:e68792.
- Huang C, Wahlund L, Dierks T, Julin P, Winblad B, Jelic V. Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: a cross-sectional and longitudinal study. Clin Neurophysiol 2000; 111:1961-1967.
- Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell 2012; 148:1204-1222.
- Huber W, Weniger D, Poeck K, Willmes K. The Aachen Aphasia Test Rationale and construct validity (author's transl). Der Nervenarzt 1980; 51:475-482.
- Humeau-Heurtier A. The Multiscale Entropy Algorithm and Its Variants: A Review. Entropy 2015; 17:3110-3123.
- Hyvarinen A, Karhunen J, Oja E. Independent Component Analysis. New York, USA, Wiley 2001.
- Iaccarino L, Chiotis K, Alongi P, Almkvist O, Wall A, Cerami C, et al. A Cross-Validation of FDG- and Amyloid-PET Biomarkers in Mild Cognitive Impairment for the Risk Prediction to Dementia due to Alzheimer's Disease in a Clinical Setting. J Alzheimers Dis 2017; 59:603-614.
- Ibanez-Molina AJ, Iglesias-Parro S, Escudero J, Differential Effects of Simulated Cortical Network Lesions on Synchrony and EEG Complexity. Int J Neur Syst 2018 [In press].
- Ikeda S, Mizuno-Matsumoto Y, Canuet L, Ishii R, Aoki Y, Hata M et al. Emotion Regulation of Neuroticism: Emotional Information Processing Related to Psychosomatic State Evaluated by Electroencephalography and Exact Low-Resolution Brain Electromagnetic Tomography. Neuropsychobiology 2015; 71:34-41.

- Jack CR Jr, Wiste HJ, Weigand SD, Therneau TM, Knopman DS, Lowe V, et al. Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50-95 years: a cross-sectional study. Lancet Neurol 2017; 16:435-444.
- Jan Verheijen J, Van den Bossche T, van der Zee J, Engelborghs S, Sanchez-Valle R, Lladó A, et al. A comprehensive study of the genetic impact of rare variants in SORL1 in European early□onset Alzheimer's disease. Acta Neuropathol 2016; 132:213-224.
- Jelic V, Johansson SE, Almkvist O, Shigeta M, Julin P, Nordberg A, et al. Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. Neurobiol Aging 2000; 21:533-540.
- Jelles B, van Birgelen JH, Slaets JP, Hekster RE, Jonkman EJ, Stam CJ. Decrease of non-linear structure in the EEG of Alzheimer patients compared to healthy controls. Clin Neurophysiol 1999; 110:1159-67.
- Jensen O, Kaiser J, Lachaux JP. Human γ-frequency oscillations associated with attention and memory. Trends Neurosci 2007; 30:317-324.
- Jeong J, Chae JH, Kim SY, Han SH. Nonlinear dynamic analysis of the EEG in patients with Alzheimer's disease and vascular dementia. J Clin Neurophysiol 2001; 18:58-67.
- Jeong J, Kim SY, Han SH. Non-linear dynamical analysis of the EEG in Alzheimer's disease with optimal embedding dimension. Electroencephalogr Clin Neurophysiol 1998; 106:220-8.
- Jeong J. EEG dynamics in patients with Alzheimer's disease. Clin Neurophysiol 2004; 115:1490-1505.
- Jin SC, Benitez BA, Karch CM, Cooper B, Skorupa T, Carrell D, et al. Coding variants in TREM2 increase risk for Alzheimer's disease. Hum Mol Genet 2014; 23:5838-5846.
- Johnson P, Vandewater L, Wilson W, Maruff P, Savage G, Graham P, et al. Genetic algorithm with logistic regression for prediction of progression to Alzheimer's disease. BMC Bioinformatics 2014; 15 Suppl 16:S11.
- Jones DK. Studying connections in the living human brain with diffusion MRI. Cortex 2008; 44:936-52.
- Josephs KA, Murray ME, Whitwell JL, Tosakulwong N, Weigand SD, Petrucelli L, et al. Updated TDP-43 in Alzheimer's disease staging scheme. Acta Neuropathol 2016; 131:571-85.
- Jung TP, Makeig S, Westerfield M, Townsend J, Courchesne E. Sejnowski TJ. Analysis and visualization of single-trial event-related potentials. Hum Brain Mapp 2001; 14:166-85.
- Kaiser J, Heidegger T, Lutzenberger W. Behavioral relevance of γ-band activity for short-term memory-based auditory decision-making. Eur J Neurosci 2008; 27:3322-3328.
- Kaplan AY, Fingelkurts AA, Borisov SV, Darkhovsky BS. Nonstationary nature of the brain activity as revealed by EEG/MEG: methodological, practical and conceptual challenges. Signal Process 2005; 85:2190-2212.
- Kaplan E. The assessment of aphasia and related disorders. Lippincott Williams & Wilkins, 1983.
- Karlstrom H, Brooks WS, Kwok JB, Broe GA, Kril JJ, McCann H, et al. Variable phenotype of Alzheimer's disease with spastic paraparesis. J Neurochem 2008; 104:573-583.
- Karrasch M, Laine M, Rinne JO, Rapinoja P, Sinervä E, Krause CM. Brain oscillatory responses to an auditory-verbal working memory task in mild cognitive impairment and Alzheimer's disease. Int J Psychophysiol 2006; 59:168-78.
- Kato T, Inui Y, Nakamura A, Ito K. Brain fluorodeoxyglucose (FDG) PET in dementia. Ageing Res Rev 2016; 30:73-84.
- Katz MJ. Fractals and the analysis of waveforms. Comput Biol Med 1988; 18:145-156.
- Keil A, Müller MM, Ray WJ, Gruber, Elbert T. Human γ band activity and perception of a gestalt. J Neurosci 1999; 19:7152-7161.
- Kertesz A, Davidson W, Fox H. Frontal behavioral inventory: diagnostic criteria for frontal lobe dementia. Can J Neurol Sci 1997; 24:29-36.
- Kim DJ, Jeong J, Chae JH, Park S, Yong Kim S, Jin Go H, et al. An estimation of the first positive Lyapunov exponent of the EEG in patients with schizophrenia. Psychiatry Res 2000; 98:177-89.
- Klass DW, Brenner RP. Electroencephalography of the elderly. J Clin Neurophysiol 1995; 12:116-31.
- Klimesch W, Doppelmayr M, Schimke H, Ripper B. Θ synchronization and α desynchronization in a memory task. Psychophysiology 1997; 34:169-176.
- Klimesch W. EEG α and θ oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Rev 1999; 29:169-195.
- Knopman DS. Diagnostic tests for Alzheimer disease: FDG-PET imaging is a player in search of a role. Neurol Clin Pract 2012; 2:151-153.
- Kobayashi N, Shinagawa S, Nagata T, Shimada K, Shibata N, Ohnuma T, et al. Usefulness of DNA Methylation Levels in COASY and SPINT1 Gene Promoter Regions as Biomarkers in Diagnosis of Alzheimer's Disease and Amnestic Mild Cognitive Impairment. PLoS One 2016; 11:e0168816.
- Koenig T, Prichep L, Dierks T, Hubl D, Wahlund LO, John ER, et al. Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 2005; 26:165-171.

- Kouzuki M, Asaina F, Taniguchi M, Musha T, Urakami K. The relationship between the diagnosis method of neuronal dysfunction (DIMENSION) and brain pathology in the early stages of Alzheimer's disease. Psychogeriatrics 2013; 13:63-70.
- Kubicki S, Herrmann WM, Fichte K, Freund G. Reflections on the topics: EEG frequency bands and regulation of vigilance. Pharmakopsychiatr Neuropsychopharmakol 1979; 12:237-245.
- Kurimoto R, Ishii R, Canuet L, Ikezawa K, Iwase M, Azechi M, et al. NeuroImage Induced oscillatory responses during the Sternberg's visual memory task in patients with Alzheimer's disease and mild cognitive impairment. Neuroimage 2012; 59:4132-40.
- Kurt P, Emek-Savaş DD, Batum K, Turp B, Güntekin B, Karşıdağ S, et al. Patients with mild cognitive impairment display reduced auditory event-related δ oscillatory responses. Behav Neurol 2014; 2014:268967.
- Labate D, Foresta FL, Morabito G, Palamara I, Morabito FC. Entropic Measures of EEG Complexity in Alzheimer's Disease Through a Multivariate Multiscale Approach. IEEE Sens J 2013; 13:3284-3292.
- Lacour A, Espinosa A, Louwersheimer E, Heilmann S, Hernández I, Wolfsgruber S, et al. Genome-wide significant risk factors for Alzheimer's disease: role in progression to dementia due to Alzheimer's disease among subjects with mild cognitive impairment. Mol Psychiatry 2017; 22:153-160.
- Langa KM, Larson EB, Crimmins EM, Faul JD, Levine DA, Kabeto MU, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. JAMA Intern Med 2017; 177:51-8.
- Latora V, Marchiori M. Efficient behavior of small-world networks. Phys Rev Lett 2001; 87:198701.
- Lehnertz K, Mormann F, Kreuz T, Andrzejak RG, Rieke C, David P, et al. Seizure prediction by nonlinear EEG analysis. IEEE Eng Med Biol Mag 2003; 22:57-63.
- Lempel A, Ziv J. On the complexity of finite sequences. IEEE Trans Inf Theory 1976; 22.75-81.
- Lenzi D, Serra L, Perri R, Pantano P, Lenzi GL, Paulesu E, et al. Single domain amnestic MCI: a multiple cognitive domains fMRI investigation. Neurobiol Aging 2011; 32:1542-57.
- Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 1995; 269:973-977.
- Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol 2013; 9:106-18.
- Liu Y, Spulber G, Lehtimäki KK, Könönen M, Hallikainen I, Gröhn H, et al. Diffusion tensor imaging and tract-based spatial statistics in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 2011; 32:1558-71.
- Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017; 390:2673-734.
- Logroscino G. The role of prevention in common neurological disorders. Oxford University Press 2017 [in press].
- Lopes da Silva F. EEG and MEG: relevance to neuroscience. Neuron 2013; 80:1112-28.
- Lopes da Silva FH, Pijn JP, Velis D, Nijssen PC. A rhythms: noise, dynamics and models. Int J Psychophysiol 1997; 26:237-49.
- Lowndes G, Savage G. Early detection of memory impairment in Alzheimer's disease: a neurocognitive perspective on assessment. Neuropsychol Rev 2007; 17:193-202.
- Makeig S, Westerfield M, Jung TP, Enghoff S, Townsend J, Courchesne E, et al. Dynamic brain sources of visual evoked responses. Science 2002; 295:690-4.
- Marnane M, Al-Jawadi OO, Mortazavi S, Pogorzelec KJ, Wang BW, Feldman HH, et al. Alzheimer's Disease Neuroimaging Initiative. Periventricular hyperintensities are associated with elevated cerebral amyloid. Neurology 2016; 86:535-43.
- Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet 2013; 382:1405-12.
- Matthews FE, Stephan BC, Robinson L, Jagger C, Barnes LE, Arthur A, et al. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. Nat Commun 2016; 7:11398.15.
- McGinnis SM. Neuroimaging in neurodegenerative dementias. Semin Neurol 2012; 32:347-60.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984; 34:939-944.
- McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7:263-269.
- Miraglia F, Vecchio F, Bramanti P, Rossini PM. EEG characteristics in "eyes-open" versus "eyes-closed" conditions: Small-world network architecture in healthy aging and age-related brain degeneration. Clin Neurophysiol 2016; 127: 1261-1268.
- Miraglia F, Vecchio F, Bramanti P, Rossini PM. Small-worldness characteristics and its gender relation in specific hemispheric networks. Neuroscience 2015; 310: 1-11.

- Miraglia F, Vecchio F, Rossini PM. Searching for signs of aging and dementia in EEG through network analysis. Behav Brain Res 2017; 317:292-300.
- Missonnier P, Deiber MP, Gold G, Herrmann FR, Millet P, Michon A, et al. Working memory load-related electroencephalographic parameters can differentiate progressive from stable mild cognitive impairment. Neuroscience 2007; 150:346-56.
- Mognon A, Jovicich J, Bruzzone L, Buiatti M. ADJUST : An automatic EEG artifact detector based on the joint use of spatial and temporal features. Psychophysiology 2011; 48:229-40.
- Morison G, Tieges Z, Kilborn K. Analysis of Electroencephalography Activity in Early Stage Alzheimer's Disease Using a Multiscale Statistical Complexity Measure. Adv Sci Lett 2013; 19:2414-2418.
- Mosher JC, Leahy RM, Lewis PS. EEG and MEG: forward solutions for inverse methods. IEEE Trans Biomed Eng 1999; 46:245-59.
- Mosher JC, Leahy RM. Source localization using recursively applied and projected (RAP) music. IEEE Trans Signal Process 1999; 47:332-340.
- Mosher JC, Lewis PS, Leahy RM. Multiple Dipole Modeling and Localization from Spatio-Temporal MEG Data. IEEE Trans Biomed Eng 1992; 39:541-557.
- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015; 131:e29-322.
- Muthukumaraswamy SD. Functional Properties of Human Primary Motor Cortex Γ Oscillations. J Neurophysiol 2010; 104:2873-85.
- Muthukumaraswamy SD. High-frequency brain activity and muscle artifacts in MEG/EEG: a review and recommendations. Front Hum Neurosci 2013; 7:138.
- Newman ME. Properties of highly clustered networks. Phys Rev E Stat Nonlin Soft Matter Phys 2003; 68:026121.
- Niedermeyer E, da Silva FL. Electroencephalography: Basic Principles, Clinical Applications, and Related Fields. Lippincott Williams & Wilkins, 2005.
- Nikolic D, Fries P, Singer W. Γ oscillations: precise temporal coordination without a metronome. Trends Cogn Sci 2013; 17:54-55.
- Nishida K, Yoshimura M, Isotani T, Yoshida T, Kitaura Y, Saito A, et al. Differences in quantitative EEG between frontotemporal dementia and Alzheimer's disease as revealed by LORETA. Clin Neurophysiol 2011; 122:1718-1725.
- Nolan H, Whelan R, Reilly RB. FASTER : Fully Automated Statistical Thresholding for EEG artifact Rejection. J Neurosci Methods 2010; 192:152-162.
- Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol 2014; 13:788-94.
- Nunez PL, Srinivasan R. A theoretical basis for standing and traveling brain waves measured with human EEG with implications for an integrated consciousness. Clin Neurophysiol 2006; 117:2424-35.
- Nunez PL. Estimation of large scale neocortical source activity with EEG surface Laplacians. Brain Topogr 1989; 2:141-154.
- Nunez PL. Toward a quantitative description of large-scale neocortical dynamic function and EEG. Behav Brain Sci 2000; 23:371-98.
- Onnela JP, Saramaki J, Kertesz J, Kaski K. Intensity and coherence of motifs in weighted complex networks. Phys Rev E Stat Nonlin Soft Matter Phys 2005; 71:065103.
- Onton J, Makeig S. High-frequency broad band modulations of electro-encephalographic spectra. Front HumNeurosci 2009; 23:3-61.
- Osipova D, Pekkonen E, Ahveninen J. Enhanced magnetic auditory steady-state response in early Alzheimer's disease. Clin Neurophysiol 2006; 117: 1990-1995.
- Ossenkoppele R, Pijnenburg YA, Perry DC, Cohn-Sheehy BI, Scheltens NM, Vogel JW, et al. The behavioral/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features. Brain 2015; 138:2732-2749.
- Panza F, Solfrizzi V, Logroscino G. Age-related hearing impairment-a risk factor and frailty marker for dementia and AD. Nat Rev Neurol 2015; 11:166-75.
- Parra MA, Abrahams S, Fabi K, Logie R, Luzzi S, Sala SD. Short-term memory binding deficits in Alzheimer's disease. Brain 2009a; 132:1057-1066.
- Parra MA, Abrahams S, Logie RH, Della Sala S. Age and binding within dimension features in visual short-term memory. Neurosci Lett 2009b; 449:1-5.
- Pascual-Marqui RD, Lehmann D, Koukkou M, Kochi K, Anderer P, Saletu B et al. Assessing interactions in the brain with exact low-resolution electromagnetic tomography. Philos Trans A Math Phys Eng Sci 2011; 369:3768-3784.
- Pascual-Marqui RD, Michel CM, Lehmann D. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int J Psychophysiol 1994; 18:49-65.
- Pascual-Marqui RD. Discrete, 3D Distributed, Linear Imaging Methods of Electric Neuronal Activity. Part 1: Exact, Zero Error Localization. 2007a; arXiv:0710.3341.

- Pascual-Marqui RD. Instantaneous and lagged measurements of linear and nonlinear dependence between groups of multivariate time series: frequency decomposition. 2007b; arXiv:0711.1455.
- Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol 2002; 24 Suppl D:5-12.
- Pascual-Marqui RD. Theory of the EEG Inverse Problem. In: 2009 Artech House B, editor. Quantitative EEG Analysis: Methods and Clinical Applications. 2009; pp. 121-40.
- Pastor P, Roe CM, Villegas A, Bedoya G, Chakraverty S, García G, et al. Apolipoprotein Eepsilon4 modifies Alzheimer's disease onset in an E280A PS1 kindred. Ann Neurol 2003; 54:163-169.
- Perrin F, Pernier J, Bertrand O, Giard MH, Echallier JF. Mapping of scalp potentials by surface spline interpolation. Electroencephalogr Clin Neurophysiol 1987; 66:75-81.
- Persson K, Barca ML, Eldholm RS, Cavallin L, Šaltytė Benth J, Selbæk G, et al. Visual Evaluation of Medial Temporal Lobe Atrophy as a Clinical Marker of Conversion from Mild Cognitive Impairment to Dementia and for Predicting Progression in Patients with Mild Cognitive Impairment and Mild Alzheimer's Disease. Dement Geriatr Cogn Disord 2017; 44:12-24.
- Peters F, Collette F, Degueldre C, Sterpenich V, Majerus S, Salmon E. The neural correlates of verbal short-term memory in Alzheimer's disease: an fMRI study. Brain 2009; 132:1833-46.
- Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018; 90:126-135.
- Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56:303-308.
- Petersen RC, Thomas RG, Aisen PS, Mohs RC, Carrillo MC, Albert MS. Randomized controlled trials in mild cognitive impairment: Sources of variability. Neurology 2017; 88:1751-1758.
- Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004; 256:183-194.
- Pfurtscheller G, Aranibar A. Event-related cortical desynchronization detected by power measurements of scalp EEG. Electroencephalogr Clin Neurophysiol 1977; 42:817-26.
- Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 1999; 110:1842-57.
- Phelps ME. PET: the merging of biology and imaging into molecular imaging. J Nucl Med 2000; 41:661-81.
- Pihlajamäki M, Jauhiainen AM, Soininen H. Structural and functional MRI in mild cognitive impairment. Curr Alzheimer Res 2009; 6:179-85.
- Pijn JP, Velis DN, van der Heyden MJ, DeGoede J, van Veelen CW, Lopes da Silva FH. Nonlinear dynamics of epileptic seizures on basis of intracranial EEG recordings. Brain Topogr 1997; 9:249-70.
- Piscopo P, Marcon G, Piras MR, Crestini A, Campeggi LM, Deiana E, et al. A novel PSEN2 mutation associated with a peculiar phenotype. Neurology 2008; 70:1549-1554.
- Pomati S, Vanacore N, Frasson P, Ghiretti R, Catricalà E, Cucumo V, et al. Free and cued selective reminding test: A validity study in subjects attending memory clinics. Alzheimers Dement 2011; 7:e17.
- Porcaro C, Tecchio F. Semi-blind Functional Source Separation Algorithm from Non-invasive Electrophysiology to Neuroimaging. Blind Source Separation, Editor Springer (Berlin Heidelberg), 2014, pp. 521-551.
- Prichep LS, John ER, Ferris SH, Rausch L, Fang Z, Cancro R, et al. Prediction of longitudinal cognitive decline in normal elderly with subjective complaints using electrophysiological imaging. Neurobiol Aging 2006; 27:471-481.
- Pritchard WS, Duke DW, Coburn KL, Moore NC, Tucker KA, Jann MW, et al. EEG-based, neural-net predictive classification of Alzheimer's disease versus control subjects is augmented by non-linear EEG measures. Electroencephalogr Clin Neurophysiol 1994; 91:118-30.
- Rait G, Walters K, Bottomley C, Petersen I, Iliffe S, Nazareth I. Survival of people with clinical diagnosis of dementia in primary care: cohort study. BMJ (Clinical research ed) 2010; 341:c3584.
- Ramyead A, Kometer M, Studerus E, Koranyi S, Ittig S, Gschwandtner U et al. Aberrant Current Source-Density and Lagged Phase Synchronization of Neural Oscillations as Markers for Emerging Psychosis. Schizophr Bull 2015; 41:919-929.
- Ravizza SM, Behrmann M, Fiez JA. Right parietal contributions to verbal working memory: Spatial or executive? Neuropsychologia 2005; 43:2057-2067.
- Rey A. L'examen psychologique dans les cas d'encéphalopathie traumatique (Les problems). Arch Psychol, 1941.
- Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 2000; 278:2039-2049.
- Ridha BH, Barnes J, van de Pol LA, Schott JM, Boyes RG, Siddique MM, et al. Application of automated medial temporal lobe atrophy scale to Alzheimer disease. Arch Neurol 2007; 64:849-54.
- Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Lads EC, Martin S. CSF tau and the CSF tau/AB ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 2017; 3:CD010803.

- Rocca WA, Boyd CM, Grossardt BR, Bobo WV, Finney Rutten LJ, Roger VL, et al. Prevalence of multimorbidity in a geographically defined American population: patterns by age, sex, and race/ethnicity. Mayo Clin Proc 2014; 89:1336-49.
- Rocca WA, Grossardt BR, Brue SM, Bock-Goodner CM, Chamberlain AM, Wilson PM, et al. Data Resource Profile: Expansion of the Rochester Epidemiology Project medical records-linkage system (E-REP). Int J Epidemiol 2018; 47:368-368.
- Rossini PM, Del Percio C, Pasqualetti P, Cassetta E, Binetti G, Dal Forno G, et al. Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. Neuroscience 2006; 143:793-803.
- Rostaghi M, Azami H. Dispersion Entropy: A Measure for Time-Series Analysis. IEEE Signal Process Lett 2016; 23:610-614.
- Rowe CC, Villemagne VL. Amyloid imaging with PET in early Alzheimer disease diagnosis. Med Clin North Am 2013; 97:377-98.
- Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. NeuroImage 2010; 52:1059-1069.
- Sachdev PS, Lipnicki DM, Kochan NA, Crawford JD, Thalamuthu A, Andrews G, et al. Cohort Studies of Memory in an International Consortium (COSMIC). The Prevalence of Mild Cognitive Impairment in Diverse Geographical and Ethnocultural Regions: The COSMIC Collaboration. PLoS One 2015; 10:e0142388.
- Sarazin M, Berr C, De Rotrou J, Fabrigoule C, Pasquier F, Legrain S, et al. Amnestic syndrome of the medial temporal type identifies prodromal AD: A longitudinal study. Neurology 2007; 69:1859-1867.
- Sarazin M, de Souza LC, Lehéricy S, Dubois B. Clinical and Research Diagnostic Criteria for Alzheimer's Disease. Neuroimaging Clin N Am 2012; 22:23-32.
- Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. New Eng J Med 2016; 374:523-32.
- Sauseng P, Griesmayr B, Freunberger R, Klimesch W. Control mechanisms in working memory: A possible function of EEG θ oscillations. Neurosci Biobehav Rev 2010; 34:1015-1022.
- Scheeringa R, Petersson KM, Kleinschmidt A, Jensen O, Bastiaansen MC. EEG α power modulation of fMRI resting-state connectivity. Brain Connect 2012; 2:254-64.
- Schellenberg GD, Montine TJ. The Genetics and Neuropathology of Alzheimer's Disease. Acta Neuropathol 2012; 124:305-323.
- Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992; 55:967-72.
- Scherg M, Berg P. Use of prior knowledge in brain electromagnetic source analysis. Brain Topogr 1991; 4:143-150.
- Schreiter-Gasser U, Rousson V, Hentschel F, Sattel H, Gasser T. Alzheimer disease versus mixed dementias: an EEG perspective. Clin Neurophysiol 2008; 119:2255-9.
- Schurmann M, Basar E. Functional aspects of α oscillations in the EEG. Int J Psychophysiol 2001; 39:151-158.
- Serra L, Cercignani M, Basile B, Spanò B, Perri R, Fada L, et al. White matter damage along the uncinate fasciculus contributes to cognitive decline in AD and DLB. Curr Alzheimer Res 2012; 9:326-33.
- Serra L, Cercignani M, Lenzi D, Perri R, Fada L, Caltagirone C, et al. Grey and white matter changes at different stages of Alzheimer's disease. J Alzheimers Dis 2010a; 19:147-59.
- Serra L, Cercignani M, Petrosini L, Basile B, Perri R, Fada L, et al. Neuroanatomical correlates of cognitive reserve in Alzheimer disease. Rejuvenation Res 2011; 14:143-51.
- Serra L, Fada L, Perri R, Spanò B, Marra C, Castelli D, et al. Constructional Apraxia as a Distinctive Cognitive and Structural Brain Feature of Pre-Senile Alzheimer's Disease. J Alzheimers Dis 2014; 38:391-402.
- Serra L, Giulietti G, Cercignani M, Spanò B, Torso M, Castelli D, et al. Mild cognitive impairment: same identity for different entities. J Alzheimers Dis 2013; 33:1157-65.
- Serra L, Mancini M, Cercignani M, Di Domenico C, Spanò B, Giulietti G, et al. Network-Based Substrate of Cognitive Reserve in Alzheimer's Disease. J Alzheimers Dis 2017; 55:421-430.
- Serra L, Perri R, Cercignani M, Spanò B, Fada L, Marra C, et al. Are the behavioral symptoms of Alzheimer's disease directly associated with neurodegeneration? J Alzheimers Dis 2010b; 21:627-39.
- Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995; 375:754-760.
- Simons S, Espino P, Abásolo D. Fuzzy Entropy Analysis of the Electroencephalogram in Patients with Alzheimer's Disease: Is the Method Superior to Sample Entropy? Entropy 2018; 20:21.
- Singer W. Neuronal synchrony: a versatile code for the definition of relations? Neuron 1999; 24:49-65.
- Singer W. The formation of cooperative cell assemblies in the visual cortex. J Exp Biol 1990; 153:177-97.

- Smailagic N, Vacante M, Hyde C, Martin S, Ukoumunne O, Sachpekidis C. 18F-FDG PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 2015; 1:CD010632.
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006; 31:1487-505.
- Smits FM, Porcaro C, Cottone C, Cancelli A, Rossini PM, Tecchio F. Electroencephalographic Fractal Dimension in Healthy Ageing and Alzheimer's Disease. PLoS One 2016; 11:e0149587.
- Sorbi S, Nacmias B, Forleo P, Piacentini S, Latorraca S, Amaducci L. Epistatic effect of APP717 mutation and apolipoprotein E genotype in familial Alzheimer's disease. Ann Neurol 1995; 38:124-127.
- Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7:280-92.
- Spillantini MG, Goedert M. Tau pathology and neurodegeneration. Lancet Neurol 2013; 12:609-22.
- Spinelli EG, Mandelli ML, Miller ZA, Santos-Santos MA, Wilson SM, Agosta F, et al. Typical and atypical pathology in primary progressive aphasia variants. Ann Neurol 2017; 81:430-443.
- Sporns O, Chialvo DR, Kaiser M, Hilgetag CC. Organization, development and function of complex brain networks. Trends Cogn Sci 2004; 8:418-25.
- Sporns O, Zwi JD. The small world of the cerebral cortex. Neuroinformatics 2004; 2:145-62.
- Sporns O. Network attributes for segregation and integration in the human brain. Curr Opin Neurobiol 2013; 23:162-71.
- Sporns O. The human connectome: a complex network. Ann N Y Acad Sci 2011; 1224:109-125.
- Srinivasan R, Winter WR, Ding J, Nunez PL. EEG and MEG coherence: measures of functional connectivity at distinct spatial scales of neocortical dynamics. J Neurosci Methods 2007; 166:41-52.
- Stam CJ, Jelles B, Achtereekte HA, Rombouts SA, Slaets JP, Keunen RW. Investigation of EEG non-linearity in dementia and Parkinson's disease. Electroencephalogr Clin Neurophysiol 1995; 95:309-17.
- Stam CJ, Jelles B, Achtereekte HA, van Birgelen JH, Slaets JP. Diagnostic usefulness of linear and nonlinear quantitative EEG analysis in Alzheimer's disease. Clin Electroencephalogr 1996; 27:69-77.
- Stam CJ, Pijn JP, Suffczynski P, Lopes da Silva FH. Dynamics of the human α rhythm: evidence for non-linearity? Clin Neurophysiol 1999; 110:1801-13.
- Stam CJ. Modern network science of neurological disorders. Nat Rev Neurosci 2014; 15:683-695.
- Stam CJ. Nonlinear dynamical analysis of EEG and MEG: review of an emerging field. Clin Neurophysiol 2005; 116:2266-2301.
- Steriade M. Corticothalamic networks, oscillations, and plasticity. Adv Neurol 1998; 77:105-34.
- Stroop J. Stroop color word test. J Exp Physiol 1935; 18:643-662.
- Takahashi T. Complexity of spontaneous brain activity in mental disorders. Prog Neuropsychopharmacol Biol Psychiatry 2013; 45:258-266.
- Talairach J, Tournoux P. Co-planar Stereotaxic Atlas of the Human Brain. Thieme Medical, New York; 1988.
- Tallon-Baudry C, Bertrand O, Peronnet F, Pernier J. Induced γ-band activity during the delay of a visual short-term memory task in humans. J Neurosci 1998; 18:4244-4254.
- Tallon-Baudry C, Bertrand O. Oscillatory γ activity in humans and its role in object representation. Trends Cogn Sci 1999; 3:151-162.
- Tan CC, Yu JT, Tan L. Biomarkers for preclinical Alzheimer's disease. J Alzheimers Dis 2014; 42:1051-69.
- Tan CH, Hyman BT, Tan JJX, Hess CP, Dillon WP, Schellenberg GD, et al. Polygenic hazard scores in preclinical Alzheimer disease. Ann Neurol 2017; 82:484-488.
- Tang M, Ryman DC, McDade E, Jasielec MS, Buckles VD, Cairns NJ, et al. Neurological manifestations of autosomal dominant familial Alzheimer's disease: a comparison of the published literature with the Dominantly Inherited Alzheimer Network observational study (DIAN-OBS). Lancet Neurol 2016; 15:1317-1325.
- Tecchio F, Porcaro C, Barbati G, Zappasodi F. Functional source separation and hand cortical representation for a brain-computer interface feature extraction. J Physiol 2007; 580:703-21.
- Teipel SJ, Kurth J, Krause B, Grothe MJ. The relative importance of imaging markers for the prediction of Alzheimer's disease dementia in mild cognitive impairment - Beyond classical regression. Neuroimage Clin 2015; 8:583-5.
- Theiler J, Eubank S, Longtin A, Galdrikian B, Doyne Farmer J. Testing for nonlinearity in time series: the method of surrogate data. Phys. Nonlinear Phenom 1992; 58:77-94.
- Tijms BM, Wink AM, de Haan W, van der Flier WM, Stam CJ, Scheltens P, et al. Alzheimer's disease: connecting findings from graph theoretical studies of brain networks. Neurobiol Aging 2013; 34:2023-36.
- Timothy LT, Krishna BM, Nair U. Classification of mild cognitive impairment EEG using combined recurrence and cross recurrence quantification analysis. Int J Psychophysiol 2017; 120:86-95.
- Tononi G, Sporns O, Edelman GM. A measure for brain complexity: relating functional segregation and integration in the nervous system. Proc Natl Acad Sci USA 1994; 91:5033-7.

- Torralva T, Roca M, Gleichgerrcht E, Bekinschtein T, Manes F. A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. Brain 2009; 132:1299-1309.
- Trambaiolli LR, Lorena AC, Fraga FJ, Kanda PAM, Anghinah R, Nitrini R, et al. Improving Alzheimer's Disease Diagnosis with Machine Learning Techniques. Clin EEG Neurosci 2011; 42:160-5.
- Tsai PH, Lin C, Tsao J, Lin PF, Wang PC, Huang NE, et al. Empirical mode decomposition based detrended sample entropy in electroencephalography for Alzheimer's disease. J Neurosci Methods 2012; 210:230-237.
- Tylová L, Kukal J, Hubata-Vacek V, Vyšata O. Unbiased estimation of permutation entropy in EEG analysis for Alzheimer's disease classification. Biomed Signal Process Control 2018; 39:424-430.
- Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 2006; 52:155-68.
- Valdés-Sosa PA, Vega-Hernández M, Sánchez-Bornot JM, Martínez-Montes E, Bobes MA. EEG source imaging with spatio-temporal tomographic nonnegative independent component analysis. Hum Brain Mapp 2009; 30:1898-910.
- van der Hiele K, Vein AA, van der Welle A, van der Grond J, Westendorp RG, Bollen EL, et al. EEG and MRI correlates of mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2007; 28:1322-9.
- van Deursen JA, Vuurman EFPM, van Kranen-Mastenbroek VHJM, Verhey FRJ, Riedel WJ. 40-Hz steady state response in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 2011; 32:24-30.
- Vecchio F, Lacidogna G, Miraglia F, Bramanti P, Ferreri F Rossini PM. Prestimulus interhemispheric coupling of brain rhythms predicts cognitive-motor performance in healthy humans. J Cogn Neurosci 2014a; 26:1883-90.
- Vecchio F, Miraglia F, Curcio G, Altavilla R, Scrascia F, Giambattistelli F, et al. Cortical Brain Connectivity Evaluated by Graph Theory in Dementia: A Correlation Study Between Functional and Structural Data. J Alzheimers Dis 2015; 45:745-56.
- Vecchio F, Miraglia F, Marra C, Quaranta D, Vita MG, Bramanti P, et al. Human brain networks in cognitive decline: a graph theoretical analysis of cortical connectivity from EEG data. J Alzheimers Dis 2014c; 41:113-127.
- Vecchio F, Miraglia F, Piludu F, Granata G, Romanello R, Caulo M, et al. "Small World" architecture in brain connectivity and hippocampal volume in Alzheimer's disease: a study via graph theory from EEG data. Brain Imaging Behav 2017; 11:473-485.
- Vecchio F, Miraglia F, Quaranta D, Granata G, Romanello R, Marra C, et al. Cortical connectivity and memory performance in cognitive decline: a study via graph theory from EEG data. Neuroscience 2016a; 316:143-50.
- Vecchio F, Miraglia,F, Bramanti,P, Rossini,PM. Human brain networks in physiological aging: a graph theoretical analysis of cortical connectivity from EEG data, J Alzheimers Dis 2014b; 41:1239-1249.
- Vecchio F, Pellicciari MC, Miraglia F, Brignani D, Miniussi C, Rossini PM. Effects of transcranial direct current stimulation on the functional coupling of the sensorimotor cortical network. Neuroimage 2016b; 140:50-6.
- Vinck M, Womelsdorf T, Buffalo EA, Desimone R, Fries P. Attentional modulation of cell-class-specific γ-band synchronization in awake monkey area v4. Neuron 2013; 80:1077-1089.
- Visser PJ, Vos S, van Rossum I, Scheltens P. Comparison of International Working Group criteria and National Institute on Aging-Alzheimer's Association criteria for Alzheimer's disease. Alzheimers Dement 2012; 8:560-3.
- Vos SJ, van Rossum IA, Verhey F, Knol DL, Soininen H, Wahlund LO, et al. Prediction of Alzheimer disease in subjects with amnestic and nonamnestic MCI. Neurology 2013; 80:1124-32.
- Vrba J, Robinson SE. Signal processing in magnetoencephalography. Methods 2001; 25:249-271.
- Wagner M, Wolf S, Reischies F, Daerr M, Wolfsgruber S, Jessen F, et al. Biomarker validation of a cued recall memory deficit in prodromal Alzheimer disease. Neurology 2012; 78:379-386.
- Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, et al. European Task Force on Age-Related White Matter Changes. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32:1318-22.
- Wallon D, Rousseau S, Rovelet-Lecrux A, Quillard-Muraine M, Guyant-Maréchal L, Martinaud O, et al. The French Series of Autosomal Dominant Early Onset Alzheimer's Disease Cases: Mutation Spectrum and Cerebrospinal Fluid Biomarkers. J Alzheimers Dis 2012; 30:847-56.
- Warrington E, James M. VOSP Visual Object and Space Perception Test Battery. TVTC Thames Valley Test Company, Bury St Edmunds, UK, 1991.
- Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. Nature 1998; 393:440-442.
- Wilmer HH, Sherman LE, Chein JM. Smartphones and Cognition: A review of research exploring the links between mobile technology habits and cognitive functioning. Front Psychol 2017; 8:605.
- Wimo A, Guerchet M, Ali GC, Wu YT, Prina AM, Winblad B, et al. The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimers Dement 2017; 13:1-7.
- Wimo A, Jonsson L, Bond J, Prince M, Winblad B. The worldwide economic impact of dementia 2010. Alzheimers Dement 2013; 9:1-11.
- Wolf A, Swift JB, Swinney HL, Vastano JA. Determining Lyapunov exponents from a time series. Phys Nonlinear Phenom 1985; 16:285-317.

- Woon, WL, Cichocki A, Vialatte T, Musha T. Techniques for early detection of Alzheimer's disease using spontaneous EEG recordings. Physiol Meas 2007; 28:335-348.
- Worsley KJ, Chen JI, Lerch J, Evans AC. Comparing functional connectivity via thresholding correlations and singular value decomposition. Philos Trans R Soc Lond B Biol Sci 2005; 360: 913-920.
- Woyshville MJ, Calabrese JR. Quantification of occipital EEG changes in Alzheimer's disease utilizing a new metric: the fractal dimension. Biol Psychiatry 1994; 35:381-7.
- Wróbel A, Ghazaryan A, Bekisz M, Bogdan W, Kamiński J. Two streams of attention-dependent β activity in the striate recipient zone of cat's lateral posterior-pulvinar complex. J Neurosci 2007; 27:2230-40.
- Xie T, He Y. Mapping the Alzheimer's brain with connectomics, Front Psychiatry 2011; 2:77.
- Xu G, Meyer JS, Thornby J, Chowdhury M, Quach M. Screening for mild cognitive impairment (MCI) utilizing combined mini-mental-cognitive capacity examinations for identifying dementia prodromes. Int J Geriatr Psychiatry 2002; 17:1027-33.
- Yang AC, Tsai SJ. Is mental illness complex? From behavior to brain. Prog Neuropsychopharmacol Biol Psychiatry 2013; 45:253-257.
- Yang AC, Wang SJ, Lai KL, Tsai CF, Yang CH, Hwang JP, et al. Cognitive and neuropsychiatric correlates of EEG dynamic complexity in patients with Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 2013; 47:52-61.
- Yao D, He B. A self-coherence enhancement algorithm and its application to enhancing three-dimensional source estimation from EEGs. Ann Biomed Eng 2001; 29:1019-1027.
- Yener GG, Başar E. Biomarkers in ADwith a special emphasis on event-related oscillatory responses. Suppl Clin Neurophysiol 2013; 62:237-273.
- Yener GG, Emek-Savaş DD, Lizio R, Çavuşoğlu B, Carducci F, Ada E, et al. Frontal δ event-related oscillations relate to frontal volume in mild cognitive impairment and healthy controls. Int J Psychophysiol 2016; 103:110-7.
- Yener GG, Güntekin B, Başar E. Event-related δ oscillatory responses of Alzheimer patients. Eur J Neurol 2008; 15:540-547.
- Yener GG, Güntekin B, Öniz A, Başar E. Increased frontal phase-locking of event-related θ oscillations in Alzheimer patients treated with cholinesterase inhibitors. Int J Psychophysiol 2007; 64:46-52.
- Yener GG, Güntekin B, Örken DN, Tülay E, Forta H, Başar E. Auditory δ event-related oscillatory responses are decreased in Alzheimer's disease. Behav Neurol 2012; 25:3-11.
- Yener GG, Kurt P, Emek-Savaş DD, Güntekin B, Başar E. Reduced visual event-related δ oscillatory responses in amnestic mild cognitive impairment. J Alzheimers Dis 2013; 37:759-67.
- Zheng L, Kong X, Cui Y, Wei Y, Zhang J, Wei W. Conversion from MCI to AD in patients with the APOE ε4 genotype: Prediction by plasma HCY and serum BDNF. Neurosci Lett 2016; 626:19-24.

Figure legends

Fig. 1. A) Extended pedigree representing known affected subjects of all families with PS1 Met146Leu mutation. B) Pedigree of the family with APP A713T mutation associates to both early and late onset phenotypes, also independently from homozygosity.

Fig. 2. The Functional Source Separation (FSS) algorithm is a new concept-source identification method with MEG/EEG/EMG, developed by LET'S. To identify the source, FSS exploits a specific functional fingerprint of the source neurodynamics -instead of the source's position-. FSS returns the source's neurodynamics in all experimental conditions of interest, together with the source scalp distribution, which is the input for the localization algorithms, if the source's position is of interest.

Fig. 3. Scheme of an automated EEG-based AD diagnosis system in the cross-validation leave-one-subject-out paradigm (Cassani et al., 2014).